THERAPY OF THE STRESS DISORDERS
ITS SCOPE AND LIMITS *

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THERAPY in the stress disorders is a new continent still largely unexplored: there are some fairly well-mapped areas, but much of it is simply blank space, with territory in between marked only by doubts, open questions, and untested hypotheses. As in any other journey of exploration, the traveller may start from one of the " coastal zones ", about which a few facts are known with reasonable certitude, and make his way inland, hoping to meet others also in quest of truth.

What I have to say here is based partly on clinical observation and partly on reflection. Most of the work of the family doctor, and of the physician at hospital, is not such that observations on it can be quantified; the contention that progress in the art of medicine can issue solely from tables of figures is, in my view, erroneous. Hamilton (1958) clothed this principle in words most admirably when he said: " Clinical observation has been the foundation of medicine, both in research and practice. It still is." In thinking about medicine, the prime need nowadays is not for statistical agility but for plain logic. To think clearly about simple things—this can be done by the family doctor, every bit as well as the laboratory worker with his complex machines, and perhaps better.

Definitions

The term *stress* is defined as the internal or resisting force brought into being in the human organism by interaction with the environment—in our society, chiefly the personal rather than the material.

A *stress disorder* is taken to mean an illness which (1) begins at a time of crisis in the patient's life, (2) shows a time correlation with situations provoking stress in the patient, and (3) clears up when the situation changes or the patient learns to adapt to it better.

I shall take the symptom of pain, and especially the syndrome of tension-pain (O'Neill 1958), to illustrate the points I have to make.

Natural History of Stress Disorder

The incidence of illnesses relative to each other is changing—some of those that formerly stood at the top of the list have fallen back, and others appear to be increasing in relation to the rest. The prevalence of stress disorder (as a single group of illnesses) emerges clearly from the Finlay (1954) survey in general practice, carried out in 1952–53; from the preliminary results of a similar survey of incidence in the office staff of a large industrial firm (some 40% of all illness reported to the medical team belonged to the stress-disorder category); and from an analysis of first attendances in 1957 in one of the medical departments of Rolls-Royce Ltd., providing a service for some 20,000 workers (out of 50,000 leading symptoms cited by the patient, 13,500 were either headache or fatigue—two of the most common stress responses in practice [A. Levin, personal communication]). Some other data point in the same direction—for example, a review of patients with dyspepsia by five family doctors in the London area, for one month in each season of the year, showed that about 70% of the disorders found on examination were disorders of adaptation and not organic disease. In any event the conclusion seems to be inescapable that the proportion of stress disorder is rising, relative to the other kinds of disease, such as infections, that were more prevalent in former days.

What happens to all this illness? Nobody knows. There have been very few skilled surveys of a fixed population which would provide any approach to an answer to this question; one of the few is the work described by J. N. Morris (1957).

Not all the illness arising out of disharmony between man and his fellow-beings comes before the doctor. I will mention here four avenues open to the patient:

1. *He Can Try to Handle it Himself*

He can try to ignore it, put up with it, accept it as " just one of those things " (the contemporary idiom for what our forebears called Fate); diminish it by comparing himself with others worse off; incorporate it into his (or her) economy of life, in the way that some women will regard the menstrual period, not as a natural biological event, but as a " being unwell ".

He can consult the apothecary, and buy drugs in the hope of relief of his pain, or insomnia, or distress; and it is, unhappily, true that anyone can walk into a chemist's and buy, without a doctor's order, drugs that are quite unsafe in the hands of a depressed person—habit-forming, and potentially lethal.

Many patients with stress disorder postpone a consultation with the family doctor because they are afraid of what he may find: believing that they have some dread disease, they avoid an examination that might reveal it.

2. *He Can Consult a Non-medical Person*

Many of the minor disorders of adaptation (such as pain in the neck of tension origin) are " worked out " through talking about personal problems to someone who is, in effect, a therapist: most commonly, the spouse; or the clergyman; or the faith-healer; or the osteopath; or indeed any of that large army of " healers " who render service to the patient through the agency of faith. One curious social phenomenon, in this area, is the size of the province of " absent healing "—where the therapist does not even see the patient, and all communication is by mail.

Case-work by social workers and almoners merits special mention. There can be no doubt that therapy by a lay person with special experience, such as an almoner, is very often of great value to the patient, and of great service to the hard-worked physician (Coles 1959). Case-work by medical students is, similarly, effective (Davies et al. 1958), and its hazards are few.

3. *He May Come, or be Sent, to Hospital*

He may present himself at the casualty department (Mestitz 1957), or be sent to outpatients by his family doctor or through the industrial medical service.

What happens when he arrives at hospital is determined to some extent by the department to which he is sent. Patients with tension pain are often sent to the orthopædic department for an opinion, or to the department of gynæcology. Now there is nothing orthopædic or gynæcological about the genesis of symptoms in patients with the tension-pain syndrome; the department of referral, it would seem, is chosen because of the site of pain rather than its ætiology. This " accident of referral " may influence the whole subsequent history of the patient, since those who attend a special department are apt to be treated by the methods which that department normally adopts. These are usually physical methods; and, while a method such as diathermy may relieve tension pain while it is being given, if

* From a Maudsley Bequest lecture delivered to the Royal Medico-Psychological Association in London on Feb. 10, 1959.

the causal stress is not removed the pain will recur when the patient is discharged. She (it is generally a she) may even be submitted to operation, and operative procedures in patients with tension pain have two untoward effects: the pain gets worse, and it becomes difficult or impossible to relieve, since the woman believes (with some justice) that if operation was thought to be necessary her medical advisers must have held the pain to be of bodily origin.

Once the patient gets to hospital, there may begin a chain referral from one department to another: aptly named by Balint (1957) the "collusion of anonymity"—neither the patient nor her doctor knowing clearly what is happening.

4. *He Ends Up in the Surgery of the Family Doctor*

Doctor and Patient

From the viewpoint of an observer looking in on the consultation from outside there seem to be two determinants which stand out above every other variable—above the illness and its type, the doctor's technical skill, the current drugs, and all the other "furniture" of medicine. These are, I believe, (1) the doctor's attitudes and motivation, and (2) the patient's attitudes and motivation.

THE DOCTOR

To begin with an example: the case of Mr. P.

He is a man of some 55 years, a senior officer of one of the nationalised services, able, thoughtful, conscientious, a "big man" in the best sense. I saw him first just after he had been discharged from hospital after a long and tedious physical malady—multiple thrombophlebitis. By then, he had been off work for two years. He was discouraged, apprehensive about the future, worried, and depressed. He felt unfit to take up his very responsible duties again. The clinical diagnosis, in short, was "agitated depression, moderate severity". I felt dubious about recommending electroplexy, as the anæsthetist might well be reluctant to give thiopentone into the vein. So I tried him on methylamphetamine, at first intravenously, and then (as this gave him too much "kick") in the muscle. This did a lot of good. He recovered his energy, his zest for life, and his confidence in his own capacity; he went back to work. Then, unluckily (as I thought) within a few months he was offered promotion. He took the new job, which carried even heavier responsibility than the old, and within weeks was back in my clinic with depressive symptoms again. Once more I tried methylamphetamine, but this time it had little effect. In the end, after much debate, we embarked on a course of electroplexy. This did dispel the depression to some extent, but he continued to feel tense, unsure of himself, and ineffective at work. There was a "vicious spiral" of anxiety—work impairment—guilt—anxiety. He needed a great deal of reassurance and moral support, and I carried him in the outpatient clinic for several months. Then one day the question of retirement on medical grounds was raised; looking back, I recall that it was I, and not he, who raised it. The patient agreed that perhaps, after all, the struggle was not worth while; perhaps it might be better to give up and go home. At his next visit, a fortnight later, the "mood of the consultation"—his and mine—had changed. I proposed that he should try carrying on a little further, in the hope that the tension and residual depression might clear of themselves. He agreed to this, too; and later that day I reflected on the decision about retirement, and came to the conclusion that it had been determined, in the main, by a state of mind in me, and not in the patient. On that day I had myself been under the weather, bored, perhaps weary with the effort of supporting a sick man, or whatever—the decision was made "in me", and not "in the situation". So, then, we changed our minds—Mr. P did not retire, and now has made an almost full recovery from his depression, and thus avoided a retirement that would certainly have been premature and ill-advised.

This is an especially simple example: the point at issue here was a single decision. But I wonder whether the course and outcome of many illnesses in the class of disorders of adaptation may be determined, not by physical or emotional forces within the patient, but by variations within the doctor, and even changes in his "universe"—his domestic life, his career and its vicissitudes, his state of health. During a spell of postinfluenzal depression, say, he may be inclined to take a gloomy view of his patients' ailments, and to make recommendations tending to be dispirited and fatalistic, rather than more sanguine and hopeful, if that is his norm.

At a former teaching hospital of mine, there came into general use a "sign for hysteria", named after the physician who first discovered it: a curling-in of the thumb, and clenching of the fist—in the doctor, not the patient. He had found that certain patients caused his fingers to behave in this way, and that these were always hysterics. Many doctors have great difficulty in the management of disorders with an undercurrent of hysteria: they become very impatient, even angry, and discharge the patient from care hastily, saying to themselves "she's swinging it", or "he's just using me". The decision as to what to do will most likely be dictated by the doctor's attitude, and not by the patient's illness. Many women with tension pain upset their doctors, and the beginner will find himself striving to suppress his annoyance, or else trying to remove the pain—a course that may have unhappy consequences, since the illness, as often as not, serves an important purpose in the patient's "life economy", and to remove it is not only unwise but unkind.

The *furor therapeuticus*, the missionary zeal of the young doctor to make the patient better: how much distress and dislocation of life-patterns this can cause! As I have found, quite a high proportion of apparently fit middle-aged men who attend dermatological clinics on account of pruritus ani come, not in order to be rid of their symptom, but for quite another reason—namely, to gain medical sanction. Any attempts to "cure" them would be misguided. It is high time that seminars were given to final-year students on the *furor therapeuticus:* some teaching on this would save them, and their patients, a deal of wasted effort and frustration.

The doctor's own philosophy of life may be one of dour moral courage: pain and hardship are a challenge—put up with it, stick it, get on with the job—and he may be inclined to apply this to patients less well equipped for the rigours of life, and to patients with bodily symptoms outside the zone of voluntary control.

THE PATIENT

What lies behind this first doctor-patient contact? Whose idea was it? The patient's, or his mother's, or his wife's? What role does he cast the doctor in? And what role does he suppose he will be playing himself? How many other people are involved? What does he hope to gain from the consultation?

I once thought that patients came to me because they wanted to "get well"—that is, to be relieved of their symptoms. My role, then, was to dispel the symptoms as briskly as I could; the more I knew about the techniques of medicine, the better doctor would I be. Now I think differently.

The relation between man and man, and even more between man and woman, is an endless series of battles, and contests for mastery. The doctor is involved in these rather more than he would like to think. Let it be presumed that adversity, and struggle, and competition, and the perpetual fencing for position and power, are a biological necessity for health and full function of the organism.

Part of the work of the family doctor, and the hospital physician for that matter, has to do with marital problems—that is, the fight between husband and wife. One or the other partner tries to bring the doctor in, as an ally, and the main drive behind the first consultation is just that: to seek help, to have relief of distress of body or mind, but also to make a new move—defensive or offensive—in the continuing game of "lifemanship" in the arena of marriage.

For example, the husband seems to his wife to be growing cold; he pays less attention to her, loses interest in coitus, spends more time away from home. His wife feels rejected and aggrieved. If the relationship between them is not such that she can "work through" her feelings with him explicitly—and very often it is not—one mode of counter-attack is that she takes ill: in this situation the complaint of pain (headache, backache, abdominal pain, and the like) must be very commonly a presenting symptom. In a review of a random sample of women attending a gynæcological outpatient clinic, Norman Morris and I found that more than a third of the series gave pain as the chief symptom (Morris and O'Neill 1958); in only a few of these was there any physical disorder adequate to account for the pain; in the remainder, the clinical picture was consistent with the diagnosis of tension pain. Where an illness, such as this, is being employed (albeit unconsciously) by the patient and she has gained some advantage by it, then plainly efforts by the doctor to cure the pain, without altering the situation which gave rise to it, will be fruitless, and may even do harm. The main risk for the doctor who is called in by one partner of an ailing marriage is, I suppose, that he will get himself entangled in the web of feeling, the "magnetic field", around each person, that he will become aroused himself, and impelled (because of his own emotional state) to take sides. If this happens without insight, his position is that of the fly in the folk-saying "come into my parlour . . .", the spider being the husband-wife unit. Their bond to each other (however much they may fight) is always stronger than their bond to him, so he is the more likely to be punished.

Illness can be, and often is, a weapon of offence—like tears in the girl—that is brought into play when other weapons have failed, or are not available. To say this is not to impute malice to the patient. The power-drive, like the sex-drive, is an instinct with its roots in the primitive core of human nature. Naturally the organism will try using illness, if it needs to—for attack, or defence, or protection, as an appeal, for rivalry with other sick people in the household, and in a multitude of other ways. Not least among these is the use of illness to provoke the doctor. A continuing illness is a silent accusation against the doctor.

The experienced family doctor, and the medical student in his first clinical year—these are, in my view, the best "natural" therapists. The doctor just qualified, and the man in a hospital job who has no outside contacts with practice, is blinkered by a preoccupation with charts and tests and the paraphernalia of hospital procedure. Taking a look forward, it seems likely that the centre of gravity of medical practice, in the years to come, will move gradually out of the hospital and into the field of the family doctor (Godber 1958): more illness will be treated at home, and the hospital service will be more concerned with investigation and diagnosis than with treatment. As this change goes on (if I am right) we shall come to feel the need for (*a*) a new set of skills for the management of the common stress disorders, and (*b*) a new set of terms and concepts with which to describe what we are doing. The diagnostic terms, for example, and the conceptual framework of mechanismic medicine have outlived their usefulness (Halliday 1948); yet there are few others to hand.

Much of the time now spent by the medical student in learning about, say, the biochemistry of bodily function is wasted: he would be much better employed looking after people, instead of tending test-tubes—visiting their homes, seeing with his own eyes how they live, and *doing* a service to the ill person. Doing is a much more valuable instrument of learning than listening.

Conclusions

The volume of illness in our society (especially metropolitan society) due to disorders that belong to the diseases of adaptation appears to be on the increase. Much of this illness is managed by the patient himself, with or without the aid of non-medical helpers. Some of it comes to the family doctor, and some to hospital. As medical education is now, the doctor-in-training is given little preparation to aid him in the diagnosis or management of these disorders. The best kind of preparation is activity—the rendering of a service under supervision to the ill person and his family.

The main determinants of the course and outcome of an illness in this group are (1) the attitudes and motivations of the doctor, and (2) the attitudes and motivations of the patient.

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HYDROFLUMETHIAZIDE
A NEW ORAL DIURETIC

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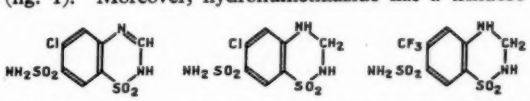
DURING the past few years many substances have been examined in an attempt to find an effective oral diuretic. Mercurial compounds given by injection have dominated diuretic therapy for nearly three decades, and it is only recently that their supremacy has been challenged by chlorothiazide. This substance was first synthesised by Novello and Sprague in 1957, and much clinical experience (Bayliss et al. 1958, Magid and Forsham 1958, Watson et al. 1958) has since shown its value. It is not, however, without untoward side-effects—in particular, the frequent production of hypokalæmia—and consequently the search for other effective agents has continued.

Two substances related to chlorothiazide—hydroflumethiazide and hydrochlorothiazide—have recently been produced, and are effective in much smaller quantity. Both these new compounds differ from chlorothiazide in having a saturated bond at position 3 : 4 in the molecule (fig. 1). Moreover, hydroflumethiazide has a trifluoro-



Chlorothiazide. Hydrochlorothiazide. Hydroflumethiazide.

Fig. 1—Chemical structure of chlorothiazide, hydrochlorothiazide, and hydroflumethiazide.

TABLE I—CONSTANCY OF URINARY EXCRETION ON CONTROL DAYS IN TWO NORMAL MEN

Subject	Age (yr.)	Weight (kg.)	Number of experiments	Urine volume (ml.)	Total sodium excretion (mEq.)	Total potassium excretion (mEq.)
1	29	65	8	522±201	60·3±16·6	41·1±6·43
2	41	78·5	10	761±151	65·4±16·1	47·0±16·1

The figures are the means and standard deviations and relate to the 10-hour period from 7 A.M. to 5 P.M.

methyl group substituted for the chlorine atom in position 6. Two preliminary clinical studies of hydroflumethiazide have already been published (Hobolth et al. 1958, Sele 1958).

Evaluation of diuretics is difficult (Spencer and Lloyd-Thomas 1953): fluctuations in the patient's response occur for no obvious reason. Initially treatment may produce a diuresis and then refractoriness ensues, and this may be unassociated with any change in serum-electrolytes or urea. Thus in the comparison of diuretics, the great variability of the background has to be considered, and, although an attempt is made to obtain a "steady" state, the steadiness is always suspect. Hence we have first studied the action of hydroflumethiazide in normal subjects, and compared it with chlorothiazide and hydrochlorothiazide. Later the drug was given to a group of patients who would ordinarily have been treated with mersalyl.

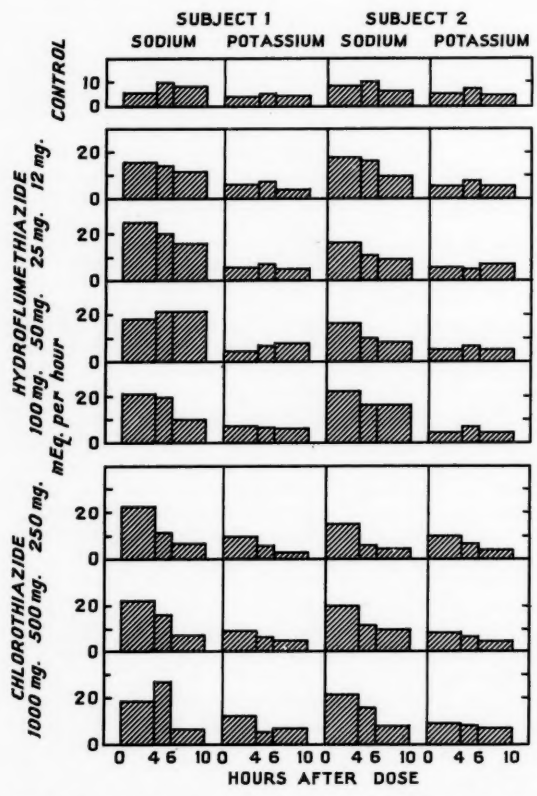


Fig. 2—Excretion of sodium and potassium by 2 normal men after various doses of hydroflumethiazide and chlorothiazide. The control excretion-rates are the means of observations made on 8 days in subject 1 and on 10 days in subject 2.

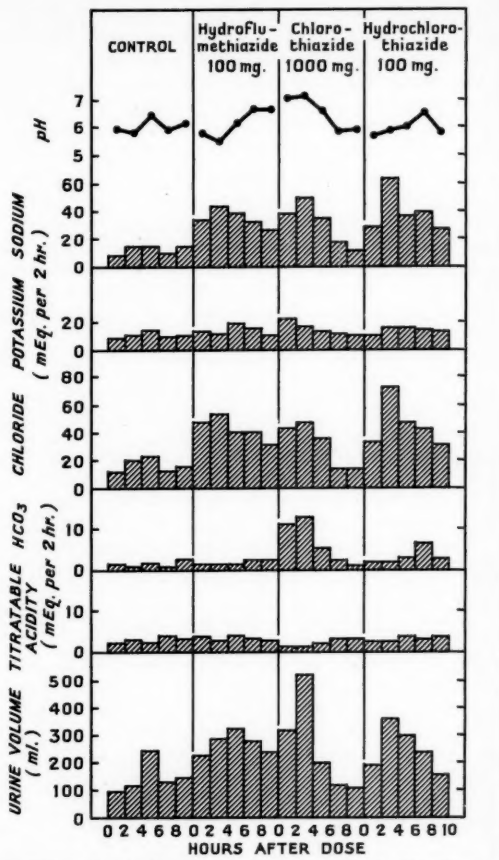

CONTROL
Hydroflu-methiazide 100 mg.
Chloro-thiazide 1000 mg.
Hydrochloro-thiazide 100 mg.
pH
SODIUM (mEq. per 2 hr.)
POTASSIUM
CHLORIDE
TITRATABLE ACIDITY
HCO3 (mEq. per 2 hr.)
URINE VOLUME (ml.)
0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 10
HOURS AFTER DOSE

Fig. 3—Effect of a single oral dose of hydroflumethiazide, 100 mg., chlorothiazide, 1000 mg., and hydrochlorothiazide, 100 mg., on urine volume and composition in 2 normal men (results given as the mean). The first column records excretion on a day on which no drug was taken.

Methods

The action of hydroflumethiazide, chlorothiazide, and hydrochlorothiazide was studied in two normal men. Urine was collected at 2-hourly intervals up to 10 hours after giving the drugs. Similar observations were also made on other days when no drugs were given (table I). The subjects carried out normal hospital and laboratory duties, but their fluid and food intake was kept as constant as possible. On this regime the two subjects had a similar sodium and potassium excretion. After giving a diuretic at least 3 days were allowed to elapse before a further experiment was carried out, to allow body composition to return to normal.

Thirty patients were studied, and all but three were initially treated in hospital. Where maintenance diuretic therapy was required, treatment was continued with hydroflumethiazide after discharge. As far as possible the patients were in a steady state before the drug was started, and all were on a normal diet without added salt (about 5 g. NaCl daily) and unrestricted fluid. The inpatients were weighed daily and urine was collected over 24-hour periods. Blood was taken for determination of electrolytes and urea before the diuretic was given, and at weekly intervals thereafter. Hæmoglobin estimation, white-cell count, and urine examination for albumin, cells, and casts were done weekly. The dose of hydroflumethiazide used in the clinical study was 50 mg. three times daily, reduced to 50 mg. daily for maintenance therapy.

Urinary sodium and potassium were estimated by flame

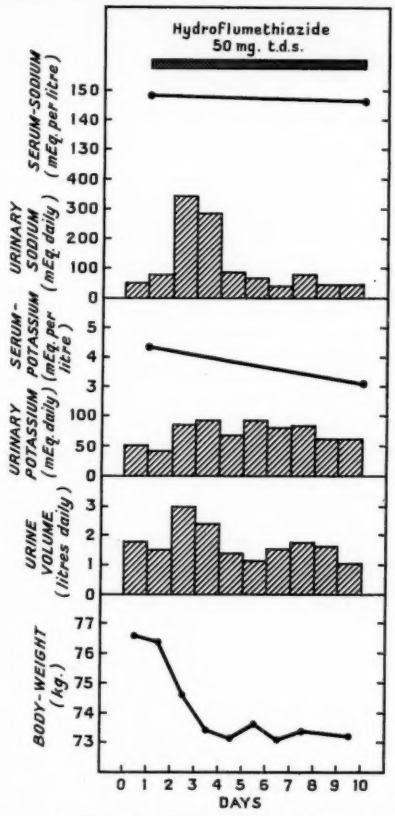


Fig. 4—Case 9 (congestive cardiac failure in ischæmic heart-disease). Effect of hydroflumethiazide on body-weight, urine volume, and urinary and serum sodium and potassium.

photometry, chloride by the potentiometric titration with silver nitrate (Sanderson 1952), bicarbonate by a microdiffusion method (Conway 1957), titratable acidity by titration to pH 7·4 with 0·1 N NaOH, and pH by a 'Marconi' pH meter. Serum-electrolytes and urea were determined by routine laboratory methods.

Results in Normal Subjects

Response to Increasing Doses of Hydroflumethiazide

Hydroflumethiazide considerably increased sodium excretion, and even with the lowest doses some effect was still apparent up to 10 hours after giving the drug (fig. 2). A comparison was made with the response to three different doses of chlorothiazide. The most conspicuous difference between the two drugs lies in the duration of action, which was considerably longer with hydroflumethiazide. With chlorothiazide even at the higher dose levels the sodium diuresis had ceased after 6 hours.

Potassium excretion was increased by both agents (fig. 2). The action of chlorothiazide was more intense, as during the first 4 hours the potassium excretion was greater with the lowest dose of chlorothiazide than with the highest dose of hydroflumethiazide.

Thus the different duration of action of the two drugs made a quantitative comparison difficult. Clearly the results and any calculated dose-response curves would depend largely on the duration of urine collection. The time relation suggested that the mechanism of action and the effect on electrolyte excretion might also differ.

TABLE II—TOTAL 10-HOUR EXCRETION OF URINARY ELECTROLYTES ON A CONTROL DAY AND AFTER HYDROFLUMETHIAZIDE, HYDROCHLOROTHIAZIDE, AND CHLOROTHIAZIDE

—	Control day	Hydroflumethiazide (100 mg.)	Hydrochlorothiazide (100 mg.)	Chlorothiazide (1000 mg.)
Sodium (mEq.) ..	53·3	168·1	185·2	144·5
Potassium (mEq.)	50·0	64·5	57·6	67·7
Chloride (mEq.) ..	73·7	204·3	216·6	147·1
Bicarbonate (mEq.)	3·5	4·6	10·6	29·2
Titratable acid (mEq.)	9·8	11·7	10·4	5·4
Water (ml.) ..	703	1299	1152	1207

Comparison of Action of Hydroflumethiazide, Chlorothiazide, and Hydrochlorothiazide

In the two normal subjects the effect of 100 mg. of hydroflumethiazide on the volume and composition of the urine was compared with the effect of 1000 mg. of chlorothiazide and of 100 mg. of hydrochlorothiazide. The results were similar in the two subjects and have therefore been presented as a mean (fig. 3 and table II).

Urine volume.—With chlorothiazide the urine flow was maximal during the 2–4 hr. collection, and by the end of the 8th hour had returned to normal. Hydrochlorothiazide and hydroflumethiazide also considerably increased urine flow, but the maximal flow was less than with chlorothiazide, and the action continued longer.

Sodium excretion.—Chlorothiazide produced a considerable increase in sodium excretion which was confined to the first 6 hours. The effect of hydrochlorothiazide and hydroflumethiazide was again more prolonged. The maximal excretion-rate of sodium for the three substances was similar, although one of the subjects produced a high peak in the 2–4 hr. collection after hydrochlorothiazide, and this resulted in a high excretion-rate for this substance (fig. 3). The total excretion over the 10 hours was substantially greater with hydrochlorothiazide and hydroflumethiazide than with chlorothiazide, a result of the briefer action of the latter.

Potassium excretion.—This was increased by all three drugs. With chlorothiazide potassium excretion was at nearly twice the control level during the first 4 hours, but later was at the normal rate. With the other two substances, the potassium excretion-rate was elevated for the first 8 hours, but it did not reach the level seen with chlorothiazide at any time.

Chloride excretion.—Changes in chloride excretion closely paralleled changes in sodium excretion (fig. 3). Chlorothiazide increased chloride excretion during the first 6 hours only, while hydrochlorothiazide and hydroflumethiazide increased it throughout the 10-hour collection period. The proportion of chloride ions to sodium ions was higher with hydrchlorothiazide and hydroflumethiazide than with chlorothiazide (table II).

Bicarbonate excretion.—The most characteristic difference among the three compounds was seen with bicarbonate excretion. This was considerably increased during the first 4 hours after chlorothiazide administration, but was not significantly altered by either hydrochlorothiazide or hydroflumethiazide.

Titratable acidity.—The excretion pattern was unaffected by hydrochlorothiazide or hydroflumethiazide. With chlorothiazide no titration was possible during the first 4 hours, as the urine was alkaline. Thereafter the excretion was as on the control day.

pH changes.—These paralleled the changes in bicarbonate excretion. Chlorothiazide differed from hydrochlorothiazide and hydroflumethiazide in producing an alkaline urine during the first 4 hours. The urinary pH changes with the latter two substances were similar to those of the control day, the urine being acid throughout with the pH rising towards the end of the collection period.

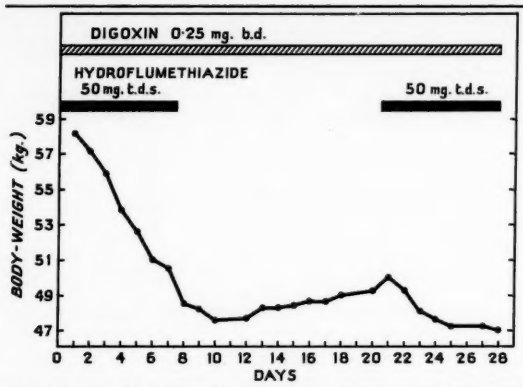


Fig. 5—Case 19 (congestive cardiac failure associated with thyrotoxicosis). Response of body-weight to two courses of hydroflumethiazide.

Clinical Trial

The results are summarised in table III. When the drug was effective, diuresis generally began as soon as treatment was started and continued until œdema had disappeared.

Pulmonary Heart-disease

Seven cases were studied. There was a good response in three patients, none in three, and no response in one until ammonium chloride was given.

The blood-urea was elevated in all those cases failing to respond. In patient no. 6, however, the blood-urea gradually fell to normal without an increase in response to hydroflumethiazide, although mersalyl produced a fair diuresis. Chlorothiazide was also tried in this man, but it failed to produce an effect.

Patient no. 2 did not respond to hydroflumethiazide at first, but after about 6 days urinary sodium excretion increased, and diuresis began. Blood-urea had fallen to normal during this time, and the patient's general condition had improved.

Patients no. 4 and 6 were given ammonium chloride, 2 g. three times daily, when hydroflumethiazide failed to act. Patient no. 4 had a fairly good diuresis with combined hydroflumethiazide and ammonium chloride, but in patient no. 6 the response was not improved. We do not know at present whether the administration of ammonium chloride when the serum-chloride is low will improve the response to hydroflumethiazide.

Ischæmic Heart-disease

Of the ten cases studied, the response was good in all but two.

A typical response is shown in fig. 4. This patient developed mild congestive failure with œdema while at rest in bed after a myocardial infarction. He was treated with hydroflumethiazide only, and there was immediately a brisk diuresis and fall in weight as œdema was lost. Hydroflumethiazide was later stopped, but œdema developed again, and maintenance therapy was necessary.

Patients no. 11 and 13, who were having attacks of left ventricular failure, had a small diuresis, and symptomatically were improved. Dyspnœa diminished, and acute attacks of dyspnœa did not recur while they were on maintenance hydroflumethiazide.

Patient no. 16 was an outpatient who had severe ischæmic heart-disease and chronic œdema controlled by two injections of mersalyl weekly. Treatment was changed to hydroflumethiazide, 50 mg. daily, and this was equally effective in controlling œdema, and he has been maintained on this now for 5 months.

Patients no. 12 and 14 both failed to respond to hydroflumethiazide, even when dosage was raised to 300 mg. daily. Patient no. 12 developed mild congestive failure after a cardiac infarction, and hydroflumethiazide did not produce a diuresis. No reason was found for this, and mersalyl produced a good diuresis and clearing of the œdema. Patient no. 14, with advanced ischæmic heart-disease, had no diuresis with hydroflumethiazide or with chlorothiazide, but showed a fair response when mersalyl was given. She later also became refractory to mersalyl, and died some 2 weeks later.

TABLE III—CLINICAL RESPONSE TO HYDROFLUMETHIAZIDE

Patient no.	Sex and age	Diagnosis	Response to hydroflumethiazide	Weight loss (kg.)	Initial serum-electrolytes and urea					Response to other diuretics	Side-effects
					Na	K	Cl	HCO_3	Urea		
1	M 64	Pulmonary heart-disease	Good	5	135	4·0	92	32	32	No comparison made	None
2	M 64	,,	Poor	0	135	4·0	94	31	50	,,	Hypokalæmia
3	F 55	,,	Good	3	141	4·5	94	34	25	,,	None
4	M 56	,,	Fair	4	136	4·3	88	30	54	Diuresis was slow until NH_4Cl 2 g. t.d.s. was given	None
5	F 68	,,	Poor	0	136	5·6	84	36	90	Mersalyl; poor	None
6	M 58	,,	Poor	0	137	3·9	88	31	68	Mersalyl; fair Chlorothiazide; poor	Hypokalæmia
7	F 46	,,	Good	2	140	4·9	87	32	32	No comparison made	None
8	F 81	Ischæmic heart-disease	Good	3	142	5·1	99	33	50	,,	None
9	M 65	,,	Good	3	148	4·3	109	..	29	,,	Hypokalæmia
10	M 74	,,	Good	5	141	4·8	97	29	25	,,	None
11	F 64	,,	Good	1	149	5·0	100	..	26	,,	None
12	M 64	,,	Poor	0	138	3·6	97	25	47	Mersalyl; good Chlorothiazide; poor	None
13	M 62	,,	Good	0	135	3·3	89	..	35	No comparison made	None
14	F 56	,,	Poor	0	134	3·6	105	25	46	Mersalyl; fair Chlorothiazide; poor	Hypokalæmia
15	M 54	,,	Good	4	132	4·6	97	..	24	No comparison made	None
16	M 54	,,	Good	0	142	5·0	101	26	39	Mersalyl; good	None
17	M 55	,,	Good	3	147	3·6	97	28	32	No comparison made	None
18	M 59	,,	Good	4	136	3·6	99	24	24	,,	None
19	F 44	Cardiac failure associated with thyrotoxicosis	Good	2	138	3·6	104	..	23	,,	None
20	F 54	,,	Good	3	145	4·0	104	24	25	,,	Hypokalæmia
21	M 52	,,	Good	4	144	3·5	100	24	22	,,	None
22	F 54	Chronic rheumatic heart-disease	Good	7	139	3·8	99	..	30	,,	None
23	F 46	,,	Good	10	139	4·4	96	23	25	,,	Transient irritating erythema
24	F 43	,,	Good	2	133	4·4	97	..	32	Mersalyl; good	None
25	F 36	,,	Good	1	138	4·0	101	..	28	No comparison made	None
26	F 34	,,	Good	0	132	3·5	97	..	24	Mersalyl; good	None
27	F 44	,,	Good	0	138	4·2	98	25	35	Mersalyl; good	None
28	F 64	,,	Poor	0	136	4·7	89	30	30	Mersalyl; poor Chlorothiazide; poor	None
29	F 46	Nephrosis	Poor	0	138	4·0	96	24	61	Chlorothiazide; poor	Hypokalæmia
30	F 26	Cirrhosis of the liver and ascites	Poor	0	130	4·0	102	23	27	Mersalyl; fair	Hypokalæmia

Cardiac Failure Associated with Thyrotoxicosis

Three cases were treated before or immediately after treatment with ^{131}I and all responded well.

Thus patient no. 19 had received ^{131}I therapy 4 weeks previously, but was still mildly hyperthyroid; on admission she was in congestive failure with considerable œdema and uncontrolled auricular fibrillation. Digoxin and hydroflumethiazide were started immediately. There was a good response (fig. 5), but evaluation of the effect of the diuretic was not possible, because of the simultaneous digoxin therapy. Hydroflumethiazide was discontinued when the œdema had disappeared. Her weight gradually rose again, however, and œdema and venous congestion reappeared. On restarting hydroflumethiazide there was a good diuresis with remission of symptoms and signs, and she was subsequently kept on a maintenance dose of 50 mg. daily.

Chronic Rheumatic Heart-disease

With one exception, all these patients responded well and no other diuretic therapy was required.

The results in an illustrative case are shown in fig. 6. This patient had chronic rheumatic heart-disease with auricular fibrillation and mitral stenosis, and was in severe cardiac failure with considerable œdema. She was in hospital for 4 days preceding the administration of hydroflumethiazide, and during this time her weight was increasing. Hydroflumethiazide produced a good diuresis and her weight fell rapidly.

Patients no. 26 and 27 were treated as outpatients. They had previously required mersalyl three times a week, but satisfactory control of œdema formation was achieved by hydroflumethiazide 50 mg. twice daily.

One patient failed to respond. She was in chronic congestive cardiac failure with gross œdema. Mersalyl and chlorothiazide were ineffective. Hydroflumethiazide produced a moderate diuresis on the first 2 days, but then ceased to act. It was found then that the patient was in an hyponatræmic state (serum-electrolytes were Na 125 mEq. per litre, K 3·2 mEq. per litre, Cl 84 mEq. per litre, and urea 35 mg. per 100 ml.). She proved refractory to all further measures and died 10 days later.

Nephrosis

The action of hydroflumethiazide was examined on one outpatient.

She had previously been on chlorothiazide, 500 mg. three times a day, but despite this had considerable œdema. Hydroflumethiazide, 50 mg. three times daily, was substituted for the chlorothiazide, but this did not produce a diuresis and weight was unchanged. On stopping hydroflumethiazide, there was no increase in œdema or in weight, and, during the 2 months in which she received no diuretic therapy, her condition has been unchanged. It seems that neither chlorothiazide nor hydroflumethiazide was capable of removing the persistent œdema in this patient, but also they were not apparently necessary to prevent further accumulation, although her dietary salt intake was only moderately restricted (about 5 g. NaCl daily).

Hepatic Cirrhosis with Ascites

The one patient studied had severe disturbance of liver function and low serum-albumin.

There was considerable ascites but no œdema. At first her urine was practically sodium-free (excretion of about 2 mEq. per 24 hr.). On the 1st day of hydroflumethiazide administration there was a moderate diuresis, and sodium excretion rose to 140 mEq. per 24 hr. On the following days sodium excretion fell, but was still considerably greater than the pretreatment level. Ascitic fluid continued to accumulate, however, and paracentesis was required. Moreover, the serum-potassium fell rapidly, and it was necessary to give potassium-chloride supplements. Subsequently an attempt to control ascites formation with hydroflumethiazide and a very low salt diet (1 g. sodium chloride daily) also failed. Mersalyl was tried, and produced a greater diuresis than hydroflumethiazide, but was also ineffective in preventing reaccumulation of ascites, and paracentesis at intervals was necessary.

Side-effects

Hydroflumethiazide was remarkably free of disturbing side-effects other than a tendency to produce hypokalæmia. There were no complaints of digestive upset, no changes in hæmoglobin or white-cell count, and no albuminuria or other urinary abnormality.

Hypokalæmia occurred in seven of our patients. It appeared within a few days or gradually over a period of several weeks. Even when the serum-potassium was less than 3 mEq. per litre, it produced no apparent effect other than a feeling of lassitude in some patients. In all cases it

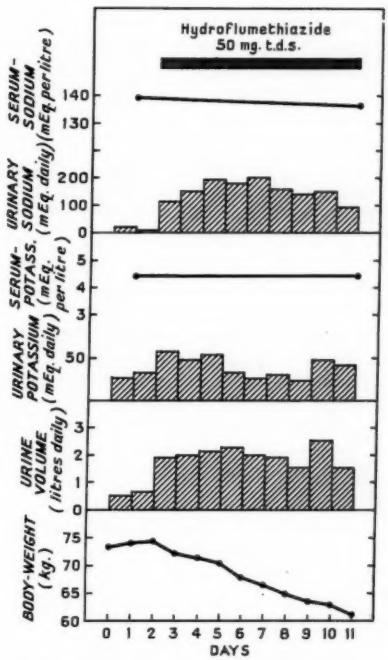


Fig. 6—Case 23 (congestive cardiac failure in chronic rheumatic heart-disease). The effect of hydroflumethiazide on body-weight, urine volume, and urinary and serum sodium and potassium.

was easily corrected by giving potassium chloride, 1 g. three times daily, and with this addition hydroflumethiazide could be continued.

Two patients complained of transient skin irritation, but this disappeared despite continuation of treatment.

Discussion

Hydroflumethiazide produced a considerable diuresis in normal subjects, and, as might be expected from its chemical structure, its action was apparently similar to that of chlorothiazide, the diuresis being associated with a high excretion of sodium and chloride.

The differences between hydroflumethiazide and chlorothiazide are in the amount required to produce a diuresis, in the action on bicarbonate excretion, and in the period of action. Hydroflumethiazide is at least ten times as effective, weight for weight, as chlorothiazide. The maximal rate of sodium excretion, however, is similar for the two drugs. Thus the only result of this increased efficiency is that a smaller quantity of hydroflumethiazide is required in treatment.

Bicarbonate excretion was increased by chlorothiazide, a well-recognised effect of the drug (Ford and Spurr 1957, Matheson and Morgan 1958), but this was not affected by hydroflumethiazide. Acetazolamide and chlorothiazide have a similar sulphonamide group and exert carbonic-anhydrase inhibitory activity. Presumably this is why bicarbonate excretion increases after chlorothiazide. Hydroflumethiazide also possesses the sulphonamide group, and probably its lack of effect on bicarbonate excretion results from the much smaller quantity used. The change in molecular configuration has enhanced activity in respect of sodium and chloride excretion without improving the carbonic-anhydrase inhibitory properties.

Hydroflumethiazide has a more prolonged action than chlorothiazide. The reason for this is unknown. The excretion pattern seen with hydrochlorothiazide was very similar to that of hydroflumethiazide, and probably their modes of action are similar.

There is no doubt from the clinical study that hydroflumethiazide is an effective diuretic in circumstances where mersalyl is ordinarily used. The response was least good in cases of pulmonary heart-disease, an observation similar to that made by Watson et al. (1958) with chlorothiazide. In those failing to have a diuresis, renal function was generally impaired, as shown by an elevated blood-urea, and this may have been partly responsible.

Only one patient with nephrosis and chronic œdema was available for study, and this patient had no diuresis with hydroflumethiazide; chlorothiazide was also ineffective. Slater and Nabarro (1958) obtained a good response using chlorothiazide in three patients with the nephrotic syndrome, and the failure of our patient to respond either to chlorothiazide or hydroflumethiazide was not explained.

The results obtained in the patient with cirrhosis of the liver with ascites were also disappointing.

In this patient, however, the severity of the condition was such that mersalyl and a very low salt diet were also incapable of controlling ascites formation. When hydroflumethiazide was first given sodium output considerably increased, and it seems likely, therefore, that a less severe case would be controlled by treatment with this diuretic.

Some cases of cirrhosis develop symptoms of hepatic precoma with chlorothiazide treatment, and, since similar results may follow acetazolamide, this untoward effect may be partly related to the carbonic-anhydrase inhibitory properties of chlorothiazide (Magid and Forsham 1958, Read et al. 1958). If so, hydroflumethiazide would probably be the preferable oral diuretic, since its carbonic-anhydrase inhibitory action is negligible. Our patient certainly showed no evidence of cerebral disturbance on 50 mg. hydroflumethiazide three times daily.

From their similar mode of action and chemical structure, one would expect that where chlorothiazide failed to produce a diuresis, hydroflumethiazide would fail also, and, in the limited number of cases where comparison was possible, this was in fact confirmed. This was not so in relation to mercurial diuretics, however, for the latter produced a good diuresis in several patients when the response to hydroflumethiazide was poor or absent. On the other hand the reverse was not true, and in all our cases where mercurial diuretics had failed, hydroflumethiazide was also ineffective. Hence mersalyl is more effective in producing a diuresis in some cases, and should be tried if hydroflumethiazide fails.

Throughout the present study, a dose of 50 mg. three times daily was used as standard initial treatment. This was sufficient to produce a good response in the majority, and in those in whom the response was poor an increase in dose had no effect. In view of the long action of the drug, however, a single dose of 100–150 mg. in the morning should be equally effective.

The only side-effect encountered with hydroflumethiazide was hypokalæmia in some patients, necessitating the administration of supplementary potassium, generally as potassium chloride, 1 g. three times daily.

Hypokalæmia is also a complication of chlorothiazide treatment and has been attributed to its carbonic-anhydrase inhibitory activity. This phenomenon also occurs, however, with hydroflumethiazide, which in the dosage used has a negligible effect on carbonic anhydrase; so it therefore seems unlikely that the hypokalæmia can be explained in this way. It is essential that the serum-potassium should be watched in patients on continuous oral diuretic therapy. In cirrhosis with fluid retention especial care has to be taken, as a considerable fall in serum-potassium may occur within a few days. In our cases a low serum-potassium was not associated with any obvious harm, but it is a hazard, especially if other drugs (such as digitalis) are being used.

Summary

Hydroflumethiazide is an oral diuretic related chemically to chlorothiazide. In comparison with chlorothiazide in normal subjects it was active in about one-tenth the dose, caused a more prolonged diuresis of water and sodium, and produced less bicarbonate but more chloride excretion. Its action closely resembled that of hydrochlorothiazide.

In a clinical study of 30 patients hydroflumethiazide was an effective diuretic in the majority. Where it failed chlorothiazide was also ineffective, but mersalyl was occasionally successful. Failure to respond was usually associated with impaired renal function, as shown by an elevated blood-urea.

Hypokalæmia in a few cases was the only side-effect encountered.

The hydroflumethiazide (' Hydrenox ') was kindly supplied by Boots Pure Drug Company, and the hydrochlorothiazide (' Esidrex ') by Ciba Laboratories.

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" . . . When she is told an operation is necessary the English patient usually very readily accepts this advice. It absolves her from any further personal responsibility for her troubles. When told that something in her domestic life is really the basis for her symptoms she often replies ' You're not trying to suggest that I am imagining all this '. A former chief of mine was just setting off to operate on a titled patient of some importance. Just as he went through the door he said ' This will be her seventeenth operation and they have all been necessary—except the first! '."—Prof. NORMAN MORRIS, *J. Coll. gen. Pract.* August, 1959, p. 235.

THE DIURETIC ACTIVITY OF HYDROFLUMETHIAZIDE

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HYDROFLUMETHIAZIDE is a recently introduced derivative of chlorothiazide which, from preliminary reports (Hobolth et al. 1958, Kobinger and Lund 1958, Sele 1958), appears to be more effective weight for weight than chlorothiazide, and to have no toxic effects.

We report here the results of volumetric and biochemical studies on seventeen patients who received 31 doses of hydroflumethiazide. Thirteen patients had congestive cardiac failure, one had cirrhosis of the liver, one had the nephrotic syndrome, one had œdema of uncertain ætiology, and one was œdema-free.

Methods

The dosage of hydroflumethiazide employed throughout was 200 mg., given by mouth at 8 A.M.

Detailed biochemical and volumetric observations were made on fourteen patients, one of whom received two doses and the remainder one dose of the drug. The urine was collected for 24 hours before the drug was given (period I), and for two consecutive 12-hour periods thereafter (periods II and III respectively), except in 3 instances where a single 24-hour collection was made after the drug. Blood samples were taken just before hydroflumethiazide was given, and 24 hours later. The urine collections were analysed in respect of volume and sodium, chloride, potassium, and inorganic phosphorus content. The urea, sodium, chloride, and potassium, and the carbon-dioxide combining-power of the blood samples was determined.

Observations were confined to precise measurements of urinary volume after administration of the drug on a further 16 occasions involving six patients (three of whom also had independent biochemical studies).

Flame photometry was used for the sodium and potassium estimations, silver-nitrate titration for chloride estimation (Wilson and Ball 1928), gas volumetric analysis for determination of carbon-dioxide combining-power (Van Slyke and Cullen 1917), the method of Archer and Robb (1925) for urea estimation, and the method of Fiske and Subbarow (1925) for inorganic phosphorus.

Results

The detailed biochemical and volumetric findings are given in the table and the figure.

Degree of diuresis.—In all instances but one (see table, case 13) a definite increase in urinary output occurred after each dose of the drug, and in most the increase was substantial. Thus in the eleven cases most intensively studied (see table) the mean urinary volume per hour was doubled in the 12 hours following the drug, and in the next 12 hours the volume was still considerably increased. A diuresis comparable with that observed in cases with cardiac œdema occurred in the patient without œdema (see figure).

Time of diuresis.—In most cases, diuresis commenced within 2 hours and was largely over within 12 hours, but in several patients diuresis continued for longer than 12 hours, or was maximal even 12–24 hours after the drug. This was particularly a feature in the patient with hepatic cirrhosis who, on two of the three occasions she received the drug, had a diuresis extending into the following day (see figure), but it was also seen in some of the patients with heart-disease.

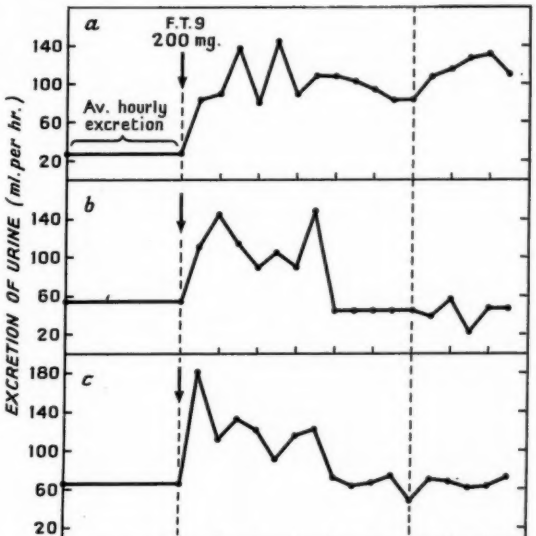
Sodium and chloride excretion.—In all fourteen patients studied biochemically urinary sodium and chloride were considerably increased after the drug. The mean increase was approximately threefold in the case of sodium (2·90 mEq. per hr. to 9·27 mEq), and fourfold in the case of chloride (2·67 mEq. per hr. to 11·58 mEq.). There was close agreement between the time of maximum diuresis and the time of maximum excretion of sodium and chloride.

Potassium excretion.—Urinary excretion of potassium was increased, but the diuresis was less than that of sodium and chloride, the mean increase in the 12 hours after the drug being about double (1·78 mEq. per hr to 3·36 mEq.).

Inorganic phosphorus.—Although there appeared to be a slight increase in the mean urinary excretion of inorganic phosphorus (21·89 mEq. per hr. rising to 29·2 mEq.), there was a wide variation, and in some instances the level was little altered or even fell.

Blood changes.—Comparison of the mean blood-levels of sodium, chloride, potassium, and urea and the alkali reserve before and after hydroflumethiazide showed no significant alteration, although there did appear to be a fall in the potassium level in some cases.

Side-effects.—No side-effects were observed in any of the patients studied.



Excretion of urine in 24 hours before (period 1), 24 hours after (period 2), and 24-36 hours after (period 3) a single dose of 200 mg. hydroflumethiazide (F.T.9)—
(*a*) Patient with hepatic cirrhosis (mean of 2 experiments).
(*b*) Patient without œdema.
(*c*) 4 patients with congestive cardiac failure (mean of 13 experiments).

Discussion

The results leave little doubt that hydroflumethiazide by mouth is an effective diuretic. Although a direct comparison was not made with chlorothiazide or with mersalyl, it was our impression that clinically a single dose of 200 mg. hydroflumethiazide produced much the same diuresis as 2 g. of chlorothiazide by mouth or 2 ml. of mersalyl intramuscularly. Probably a greater diuresis could be obtained with a higher dosage of hydroflumethiazide (e.g., 300 or 400 mg.), but since the diuresis following 200 mg. is frequently prolonged, any advantage from a higher urinary output might be offset by interference with sleep. For the same reason divided doses of hydroflumethiazide were not employed.

The mode of action appears to be the same as that of chlorothiazide—namely, an osmotic diuresis consequent upon an increased urinary excretion of sodium and chloride, and, to a lesser extent, of potassium.

In the short-term experiments performed there was no significant alteration in the blood-levels of sodium,

DETAILED VOLUMETRIC AND BIOCHEMICAL DATA ON URINE AND BLOOD IN FOURTEEN PATIENTS BEFORE AND AFTER 200 MG. OF HYDROFLUMETHIAZIDE

Case no.	Sex	Age (yr.)	Diagnosis	Period of study*	Urine						Blood (plasma)				
					Vol. (ml.)	Vol. (ml. per hr.)	K (mEq. per hr.)	Na (mEq. per hr.)	Cl (mEq. per hr.)	Inorganic phosphorus (mg. per hr.)	K (mEq. per litre)	Na (mEq. per litre)	Cl (mEq. per litre)	Alkali reserve (mEq. per litre)	Urea (mg. per 100 ml.)
1	M	56	Cor pulmonale .. .. Congestive cardiac failure	I	1100	45·8	2·60	4·81	6·00	24·50	5·0	126·0	91·0	29·01	34·0
				II	1230	102·5	4·15	14·70	17·80	39·00					
				III	520	43·3	2·20	5·33	5·27	19·36	4·5	142·3	82·4	29·47	34·5
2	F	68	Essential hypertension .. Congestive cardiac failure	I	1815	75·5	1·91	2·45	1·51	15·50	5·2	130·6	91·6	25·45	33·0
				II	1050	87·5	2·71	5·49	7·31	12·50					
				III	1460	121·5	2·49	6·50	6·15	20·70	4·8	140·0	95·6	25·90	30·0
3	F	56	Diabetes mellitus .. Nephrotic syndrome ..	I	1540	64·2	0·92	0·85	0·71	20·70	3·8	128·5	92·6	20·10	93·0
				II	770	64·2	0·83	1·53	1·10	15·90					
				III	1020	85·0	0·87	2·76	1·60	18·60	4·6	130·8	95·0	20·58	79·2
4	F	67	Myocardial ischæmia .. Congestive cardiac failure	I	980	40·8	1·31	1·07	1·10	15·00	4·6	133·0	94·2	21·90	23·0
				II	1090	90·7	3·18	7·62	9·89	11·80					
				III	604	50·3	1·83	5·17	5·75	19·85	4·2	126·0	89·2	22·57	20·0
5	M	43	Œdema of uncertain origin (? cardiac)	I	645	26·9	1·48	3·43	4·37	31·20	4·8	119·0	101·2	27·68	28·5
				II	1210	100·7	3·53	15·29	18·82	45·80					
				III	800	66·7	3·53	7·46	9·17	60·30	4·7	130·5	97·2	30·60	29·0
6	M	64	Myocardial infarction .. Congestive cardiac failure	I	1190	49·6	5·80	4·17	4·30	37·30	4·3	114·1	90·6	27·23	45·0
				II	1890	157·4	3·78	13·90	16·69	37·10					
				III	970	80·7	1·77	5·81	6·08	22·00	4·1	128·4	89·2	23·21	41·0
7	F	40	Hepatic cirrhosis ..	I	1510	62·9	2·24	4·99	3·26	28·50	3·8	135·2	106·4	21·37	23·0
				II	975	81·3	2·44	9·34	11·02	24·40					
				III	1230	102·5	3·38	10·43	11·34	36·40	3·6	144·5	106·0	22·32	18·0
8	M	64	Myocardial ischæmia .. Congestive cardiac failure	I	840	35·0	0·65	4·48	4·20	5·95	4·5	140·0	98·8	24·30	30·0
				II	545	45·4	0·75	6·84	8·36	5·76					
				III	1470	122·5	1·41	12·87	12·49	14·95	4·8	135·3	99·2	27·90	32·0
9	M	71	Cor pulmonale .. .. Congestive cardiac failure	I	240	10·0	0·31	0·06	0·07	13·10	4·8	142·2	99·2	26·35	31·0
				II	330	27·5	2·86	1·76	3·52	19·70					
				III	355	29·6	2·60	1·86	4·05	19·10	3·9	128·3	90·8	25·35	33·0
10a	M	52	Myocardial infarction .. Congestive cardiac failure	I	1370	57·1	1·97	5·47	4·71	27·20	4·9	119·0	94·0	25·21	40·0
				II	1540	120·2	8·35	17·63	25·62	81·00					
				III	790	65·7	2·76	6·60	8·72	33·61	3·7	116·5	87·2	31·23	35·3
10b	„	„	„ „ „	I	1325	55·2	0·99	1·38	0·24	25·60	3·9	133·0	91·2	29·01	34·3
				II	1650	137·5	2·82	8·66	7·00	30·70					
				III	1005	83·7	1·83	3·03	3·15	25·15	4·0	130·9	89·2	31·23	30·0
11	F	49	Essential hypertension .. Congestive cardiac failure	I	1080	45·0	1·19	1·64	1·60	18·00	5·1	123·7	99·6	25·40	30·2
				II	1460	121·5	4·87	8·52	11·82	26·75					
				III	725	60·4	2·10	4·08	5·54	16·10	3·6	116·5	101·6	24·62	33·5
Mean values of above 12 studies ..				I		47·33	1·781	2·900	2·673	21·889	4·56	128·69	96·87	25·25	37·08
				II		94·70	3·356	9·273	11·579	29·201					
				III		76·01	2·231	5·992	6·609	25·510	4·21	131·67	93·55	27·25	34·97
Range				I		10·0–75·50	0·31–5·80	0·06–5·47	0·07–6·00	5·95–37·30	3·8–5·2	114·1–142·2	90·6–106·4	20·10–29·01	23·0–93·0
				II		27·5–157·4	0·75–8·35	1·53–17·63	1·10–25·62	5·76–81·00					
				III		29·6–122·5	0·87–3·53	1·86–12·87	1·60–12·49	14·95–60·30	3·6–4·8	116·5–144·5	89·2–106·0	20·58–31·23	18·0–79·2
12	M	50	Myocardial infarction .. Congestive cardiac failure	I	1930	80·4	2·41	7·31	4·25	21·60	4·0	140·0	102·0	23·20	44·5
				II & III	2570	107·0	1·61	14·72	17·25	27·30	4·3	133·0	95·4	23·43	36·0
13	F	67	Pernicious anæmia .. Congestive cardiac failure	I	1040	43·3	1·02	4·35	4·87	16·45	4·2	132·0	103·2	22·32	19·0
				II & III	1165	48·6	0·86	6·57	7·35	8·12	5·4	126·0	96·5	26·80	25·5
14	F	61	Myocardial ischæmia .. Congestive cardiac failure	I	980	40·8	1·06	2·76	2·22	16·75	4·4	130·7	90·0	29·82	31·0
				II & III	2315	96·3	2·79	7·86	9·06	20·60	4·8	132·8	86·8	32·20	30·0
Mean values of above 3 studies ..				I		54·83	1·393	5·140	3·780	18·267	4·20	134·23	98·40	25·137	31·50
				II & III		83·93	1·753	9·717	11·220	18·673	4·83	130·60	92·60	27·473	30·50
Range				I		40·8–80·4	1·02–2·41	2·76–7·31	2·22–4·87	16·25–21·6	4·0–4·4	130·7–140·0	90·0–103·2	22·32–29·82	19·0–44·5
				II & III		48·6–107·0	0·86–2·79	6·57–14·72	7·35–17·25	8·12–27·30	4·3–5·4	126·0–133·0	86·8–95·6	23·43–32·20	25·5–36·0

* Period I = 24 hours before drug given.
„ II = 0–12 hours after drug.
„ III = 12–24 hours after drug in case of urine, 24 hours after in the case of blood.

chloride, or potassium, but, in the case of potassium at least, a supplement by mouth would probably be advisable if therapy were long-continued.

We can offer no firm explanation for the apparently prolonged action of hydroflumethiazide in the patient with hepatic cirrhosis. But this has also been seen with chlorothiazide, and it was suggested that hepatic dysfunction may delay the action of the diuretic, either because of slower absorption or because of impaired metabolism (Watson et al. 1958).

Summary

The diuretic activity of 200 mg. of hydroflumethiazide by mouth was studied on 31 occasions in seventeen patients, of whom sixteen had œdema from various causes, and one was œdema-free. Detailed volumetric and biochemical observations revealed that the usual pattern of response was a substantial increase in urinary volume, associated with an increased urinary excretion of sodium and chloride, and, to a lesser extent, of potassium. In most cases the diuresis was largely over within 12 hours, but in some the diuresis was either more prolonged, or occurred after several hours had elapsed No toxic effects were observed.

We wish to thank Prof. L. J. Davis for encouragement throughout this study. Hydroflumethiazide was supplied by Boots Pure Drug Co., Ltd. (' Hydrenox ').

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HYDROFLUMETHIAZIDE
A NEW ORAL DIURETIC

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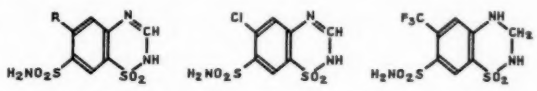
CHLOROTHIAZIDE was first described by Beyer et al. (1957) and by Novello and Sprague in 1957. Several workers (Bayliss et al. 1958a, Ford et al. 1958, Freis et al. 1958, Slater and Nabarro 1958) have reported on its use both as a diuretic and in potentiating the action of ganglion-blocking agents.

The effectiveness of chlorothiazide has resulted in a search for other potent compounds derived from the benzothiadiazine-1, 1-dioxides. One of the most promising is 6-trifluoromethyl-7-sulphamyl-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide or hydroflumethiazide. Chemically this differs from chlorothiazide in that the thiadiazine ring is saturated and the chlorine atom is replaced by a trifluoromethyl group (fig. 1). In other compounds the introduction of the trifluoromethyl group is said to reduce toxicity and increase potency (Moyer and Connor 1958).

Preliminary reports of the successful use of hydroflumethiazide have been published in Scandinavia (Hobolth et al. 1958, Sele 1958). In this paper I compare its diuretic action with that of chlorothiazide in three normal subjects and five patients with œdema, and briefly describe its clinical use in a further eight patients with œdema from various causes.

Normal Subjects

The normal subjects were two men and one woman. On the day before the experiment each had approximately the same



The Benzothiadiazine-1,1-dioxides. **Chlorothiazide.** **Hydroflumethiazide.**

Fig. 1—Structure of chlorothiazide and hydroflumethiazide.

food and fluid intake and then fasted overnight. The overnight urine was discarded, and urine was collected hourly for the next 14 hours. The subjects drank 200 ml. of water, 2 hours and 1 hour before taking a varying dose of either chlorothiazide or hydroflumethiazide, and thereafter drank a volume of water equal to the quantity of urine voided in the previous 60-minute period.

Throughout the experiment the subjects remained in the metabolic ward (which is temperature-controlled and air-conditioned) although they were not necessarily at rest. The volume of each sample of urine was measured, and its pH estimated immediately. Chemical estimations of urinary sodium, potassium, and chloride were carried out as soon as possible. Sodium and potassium were estimated by flame photometry, and urinary chlorides by the Volhard procedure. Urinary pH was measured by means of a Pye pH meter.

Fig. 2 shows typical results of giving a potent dose of hydroflumethiazide. There is clearly a diuresis, accompanied by striking increases in sodium and chloride excretion, and variable but less marked increases in potassium excretion. A similar pattern was obtained in all subjects with both hydroflumethiazide and chlorothiazide.

Table I shows the average changes in urinary flow-rate and electrolyte excretion with differing doses of the two compounds. Dosage-response curves (fig. 3) suggest that the maximum effective dose of hydroflumethiazide is about 150–200 mg. At lower dosage levels there is a roughly linear

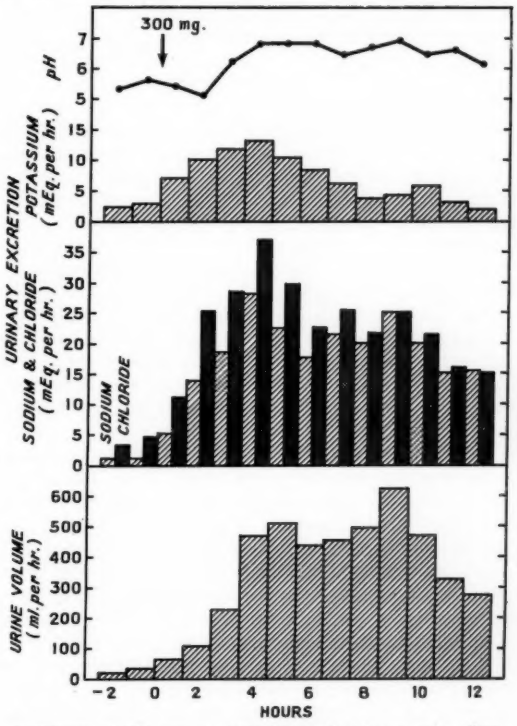


Fig. 2—Effects of 300 mg. of hydroflumethiazide on urine flow, electrolyte excretion, and pH in a normal subject.

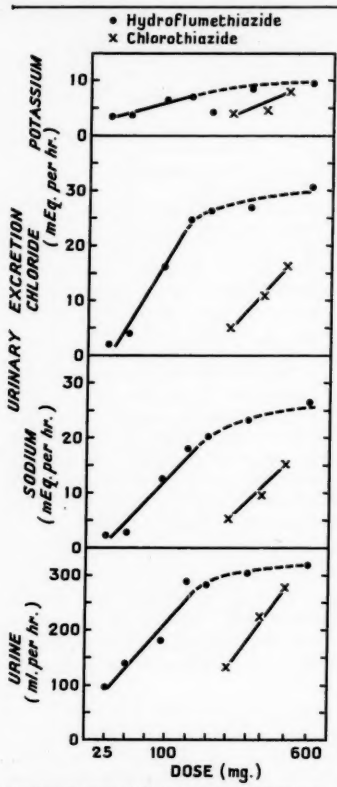


Fig. 3—Effects of differing doses of hydroflumethiazide and chlorothiazide on urine-flow and electrolyte excretion—average of the results on three normal subjects.

relation between the log. dose and the mean sodium and chloride excretion, but this is not so obvious in the case of potassium excretion.

Fig. 3 shows that for sodium and chloride excretion in these normal subjects 100–150 mg. of hydroflumethiazide is equivalent to about 500 mg. of chlorothiazide.

In each case diuresis commenced within 2 hours of administration by mouth, and did not always fully subside within 12 hours. There appeared to be two peaks of diuresis, one at about 4 hours, and a second peak at 8–9 hours.

The blood-pressure was recorded hourly during these experiments, but no statistically significant fall was noted in the three normotensive subjects.

TABLE I—AVERAGE URINE AND ELECTROLYTE EXCRETION PER HOUR OVER 12 HOURS FOR THREE NORMAL SUBJECTS

Dose (mg.)	Urine (ml. per hr.)	Na (mEq. per hr.)	K (mEq. per ml.)	Cl (mEq. per ml.)
Hydroflumethiazide:				
25	96·7	2·1	3·7	1·9
50	140·8	2·6	3·9	4·0
100	180·0	12·2	6·5	16·1
150	286·8	18·1	6·9	24·7
200	283·3	20·6	4·2	26·1
300	305·6	23·4	8·6	27·0
600	320·0	26·9	9·1	30·8
Chlorothiazide:				
250	130·0	5·4	4·1	5·1
375	224·9	9·6	4·2	11·2
500	276·3	15·5	7·9	16·6

TABLE II—AVERAGE DAILY INCREASE IN URINE AND ELECTROLYTE EXCRETION IN FIVE PATIENTS WITH ŒDEMA

Diuretic	Urine (ml. per day)	Na (mEq. per day)	K (mEq. per day)	Cl (mEq. per day)
Hydroflumethiazide (150 mg. b.d.)	529	65·1	51·5	108·7
Chlorothiazide (500 mg. b.d.)	579	52·4	51·2	77·8

Drugs commenced alternating for 4-day periods with 4-day control periods between.

Patients with Œdema

Hydroflumethiazide was given to thirteen patients, twelve with œdema due to various forms of heart-disease, and one with nephrosis. A response was obtained in all of them and in five it was possible to compare the effects with those of chlorothiazide. Treatment was given with one or other drug for 4-day periods, with intervals between treatment for equilibration, and the increase of flow-rate and electrolyte excretion over control values was compared (table II). Clinically 150 mg. of hydroflumethiazide twice daily is approximately equivalent to 0·5 g. of chlorothiazide twice daily as regards increasing both urine flow and electrolyte excretion (table II). Acute experiments similar to those outlined above were performed on patients with œdema, and produced similar results (fig. 4).

The only untoward effect noted was that two patients complained of epigastric pain after taking hydroflumethiazide. A similar effect has been seen after chlorothiazide. Hence the tablets should be taken with food if possible.

During treatment no changes were noted in the blood-urea, plasma-proteins, or platelet-counts. So far no patients have developed symptoms of hypokalæmia, although in two the serum-potassium fell to 3·2 mEq. and 3·3 mEq. per litre. In view of this, and because of the structural similarity to chlorothiazide, potassium supplements were given to patients having treatment for more than a short time. One patient with heart-failure and auricular fibrillation, controlled with digitalis, developed digitalis intoxication after 7 days' hydroflumethiazide therapy.

Two patients with malignant hypertension, requiring ganglion-blocking agents, were given hydroflumethiazide and the fall in their blood-pressure was comparable to that obtained with an equivalent dose of chlorothiazide.

Discussion

Since hydroflumethiazide may act for 12 hours or more, a single daily dose of 150–300 mg. may perhaps suffice. With a single dose there appear to be two peaks of diuresis—at about 4 hours and 9 hours. A similar effect was noted with chlorothiazide in similar experiments carried out by Bayliss et al. (1958b), and was also seen in the present

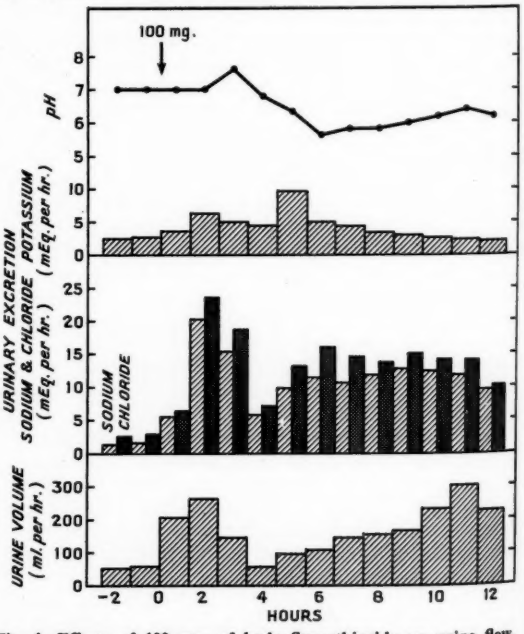


Fig. 4—Effects of 100 mg. of hydroflumethiazide on urine flow, electrolyte excretion, and pH in a patient with congestive heart-failure.

subjects with chlorothiazide. In some cases the first peak was associated with a relatively greater increase in potassium excretion and a rise in the urinary pH, and was probably due to an initial carbonic-anhydrase inhibitory effect, but this was not always conspicuous. Thus, like chlorothiazide, hydroflumethiazide inhibits carbonic anhydrase, but this action is neither powerful nor consistent.

Clinical experience with thirteen patients with œdema of varying ætiology has shown that, as a diuretic, hydroflumethiazide is as effective as chlorothiazide. The suggestion that it is less likely to cause excessive loss of potassium is not supported by the present results, from which it seems that potassium supplements are required when it is given for more than a few days. Like chlorothiazide, hydroflumethiazide has no effect on the blood-pressure of normotensive subjects, but in patients with malignant hypertension it probably potentiates ganglion-blocking agents.

Summary

Hydroflumethiazide has been used in three normal subjects and in thirteen patients with œdema.

The action is similar to that of chlorothiazide, and comparison of the two compounds suggests that 150 mg. of hydroflumethiazide is about equivalent to 500 mg. of chlorothiazide.

The maximum effect with hydroflumethiazide appeared to be obtained with about 200 mg. Below this dosage the response was proportionate to the log. of the dose.

The diuresis lasted for about 12 hours, or sometimes slightly longer.

Slight side-effects, similar to those described for chlorothiazide, were observed.

I wish to express my thanks to the physicians of the General Infirmary for access to patients; to Prof. R. E. Tunbridge for his encouragement and advice; to Sister Thwaites and the staff of the metabolic ward for their assistance with the collection of specimens; and to Dr. E. V. B. Morton (Boots Pure Drug Co.) for the supply of hydroflumethiazide.

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ACUTE ANHIDROTIC HEAT EXHAUSTION

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IN the new nomenclature for heat illness proposed by a subcommittee of the Climatic Physiology Committee of the Medical Research Council (1958), three categories of heat illness are distinguished in which diminution of sweating is prominent.

1. *Heat stroke.*—". . . Characterised by very high body temperature and profound disturbances, including delirium, convulsions, and partial or complete loss of consciousness . . ."

2. *Heat hyperpyrexia.*—" Attributable to impaired function of the heat regulating mechanism, but without the characteristic features of heat stroke. Arbitrarily defined as a temperature above 106°F . . ."

3. *Anhidrotic heat exhaustion.*—Heat exhaustion, type II (Ladell, Waterlow, and Hudson 1944); tropical anhidrotic asthenia (Allen and O'Brien 1944); thermogenic anhidrosis (Wolkin, Goodman, and Kelley 1944); anhidrotic heat exhaustion (Horne and Mole 1950). " Attributable to ' chronic ' sweating deficiency, nearly always preceded by severe prickly heat; usually associated with characteristic skin changes. . . . Very slow return to normal sweating (many weeks)."

Thus anhidrotic heat exhaustion, first described in the second world war and variously named by different authors, has been accepted as a clinical entity.

On the basis of this new nomenclature an attempt was made to classify the Army cases of heat illness in Aden in the two months September–October, 1958, when 70% of the hospital heat-illness admissions for the year occurred. A group of cases was seen in which cessation of sweating preceded all symptoms but which lacked the distinguishing features of any of the three recognised categories of anhidrotic heat illness. This observation suggested that the present classification might be incomplete; and so, though facilities for detailed analysis were limited, these cases are reported in the hope that this type of illness may be prevented. Also, before the next version of the International Statistical Classification, there is time, as the Climatic Physiology Committee remarked, " for experience to be gained in the usefulness of these proposals and for new suggestions to be brought forward ".

Clinical Features of the Acute Anhidrotic Cases

Twenty-nine Army cases of heat illness were admitted to hospital in the two months. These included five cases of borderline heat hyperpyrexia, two cases of heat stroke, and two cases of heat syncope. Twelve of the remainder possessed a feature not previously emphasised—namely, cessation of sweating without the accepted signs of hyperpyrexia or heat stroke. In response to questions all these patients said that they stopped sweating before they noticed any symptoms. This had happened between 1 and 28 hours before admission (mean 9 hours).

Though this important observation was made by the patients themselves, there seems no reason to doubt its reliability. Any reduction in sweating was likely to be noticed at once by the subjects and their companions, because the effective temperature while men worked in the sun often exceeded 90°F and the globe thermometer readings in the sun were sometimes above 130°F. In these circumstances continuous sweating was necessary to maintain thermal equilibrium, even in subjects at rest. Because of the high humidity (60%) sweat evaporated only slowly and the skin was continuously moist. All these patients stated that they had not sweated since the cessation, though they had not been capable of exertion which might have provoked sweating.

In eleven cases sweating failed during severe exertion; the other patient was first aware of its absence when he rested in his tent after exertion. Six patients collapsed shortly after the cessation of sweating and were sent directly to hospital. Six of the twelve patients did not report sick immediately but lay down in their tents. They were admitted to hospital between 8 and 28 hours after the apparent cessation of sweating.

When admitted to hospital all twelve appeared incapable of physical exertion. They were drowsy and some were mildly confused. One was grossly uncooperative, but his unit medical officer had seen him behave hysterically on previous occasions. They all seemed to want to lie down in the coolest darkest corner they could find. They had loss of appetite and several needed encouragement before they drank. The skin was in all cases hot, flushed, and

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dry by comparison with other hospital patients. There was no evidence of prickly heat (papules, vesicles, desquamation, or mammillaria).

The average oral temperature on admission was 100·4°F (range 99·2–102°F). In the six in whom it was recorded in the medical-inspection room within half an hour of reporting sick, the oral temperature did not exceed 102·0°F.

In hospital, oral temperatures after 3 minutes' supervised nose-breathing were taken instead of rectal temperatures, partly for convenience and partly because it has been shown (Gerbrandy et al. 1954) that at rest oral temperatures may reflect changes in arterial blood temperatures more accurately than the rectal temperature. Five patients were breathing deeply and irregularly on admission, but the depth and rate could be controlled voluntarily. In three patients who were overbreathing, the rectal temperature was not more than 0·8°F higher than the oral temperature taken at rest after 3 minutes' nose-breathing.

The pulses were of good volume, the mean rate 15 minutes after admission was 90 per minute (range 80–108). Blood-pressures recorded with the patients lying ranged from 105/65 to 130/80. Because of unsteadiness, all patients needed assistance on standing to be weighed, but none fainted. A pint of hot tea was given shortly after admission to six patients. In all six this failed to produce the generalised sweating which is the normal response under these conditions, though in four patients mild facial sweating resulted.

Conditions Before Admission

Climate

Eleven out of the twelve cases occurred between Sept. 8 and 28. The shade dry-bulb maximum temperature recorded at the Khormaksar Meteorological Office 4 miles from the hospital was 100°F or over on five consecutive days ending Sept. 3, but fell before these cases occurred. For Sept. 8 to 28 the mean morning shade temperatures at Khormaksar, during the hours of 0800 to 1300 when the soldiers worked, were dry-bulb 93°F and wet-bulb 82°F, and the means of maximum daily temperatures were dry-bulb 96°F, wet-bulb 84°F. The mean morning effective temperature was 83°F in the shade but nearly 10° higher in the sun. 80°F was the highest effective temperature which Yagloglou and Miller (1925) considered could be endured without harm by those doing heavy work.

Acclimatisation

All patients had been in Aden for less than two weeks, having arrived from the United Kingdom by sea, via the Suez Canal. None had previous experience of tropical climates.

Living Accommodation

All lived in canvas tents.

Water and Salt Supplies

Ten patients lived in a large transit camp where the water-supply was distasteful. Seven stated that they drank as little of the water as they could, and estimated that their fluid intake averaged only 4–7 pints daily. As each man took four salt tablets daily and much salt was added in the cooking, the total dietary salt approached 21 g. daily.

Occupation

Six subjects were infantrymen undergoing graded training, one was a driver, one a clerk, and one a cook. Two were R.A.M.C. orderlies who had committed the indiscretion of sunbathing within 3 days of arrival in Aden; both had moderate erythema without blistering, which was unlikely to have caused the sudden cessation of sweating, though it may have contributed to it. One of the infantrymen was admitted to hospital 5 days after arrival in Aden and again 8 days later; on both occasions he stated he stopped sweating on route marches and later had collapsed. The intelligence of the subjects was below average in that several failed to observe commonsense precautions to avoid heat illness.

Age

All were under the age of 22.

Management and Observations in Hospital

All patients were placed in a hospital ward with roof fans; no special measures were taken to cool them.

Dry-bulb and wet-bulb shade temperature recordings were made at the hospital between 0800 hours and 1300 hours in the morning on five consecutive days at the end of September. The means of these recordings were 2° and 1°F lower than corresponding mean values obtained from the meteorological office at Khormaksar.

The patients were encouraged to drink. They were examined at intervals in an attempt to detect the time of onset of recovery of sweating.

There were practical difficulties in measuring the water and salt balance, but some information was obtained.

Water Balance

The average weight gain over the first 24 hours after admission in eight cases in which measurements were possible was 1·22 kg. (range 0·02–3·06 kg.). Because no account was taken of fluid drunk after the cessation of sweating and before admission, this weight gain did not fully indicate the degree of water depletion. These findings suggest that most of the men had moderate water depletion.

The mean fluid intake of the same eight patients over the first 24 hours after admission was 3·2 litres (range 1·8–4·1) and the mean urine output was 0·85 litres (range 0·27–1·32). None of the patients had noted polyuria before admission, but in the first 24 hours in hospital the urine output of those patients admitted late was greater than that of the patients admitted soon after cessation of sweating.

Salt Balance

The mean plasma-chloride level in five cases in which it was determined on admission was 104 mEq./litre (range 97–111 mEq.). The chloride concentration of the first urine specimen passed after admission was greater than 2 g. per litre (Fantus 1936) in eleven cases and greater than 5 g. per litre in six. No patients gave a history of salt cramps and none had cramps after admission, despite drinking freely. Salt deficiency therefore is unlikely to have been a factor in these cases.

Evidence was obtained that, under conditions such as existed in Aden, a urinary chloride concentration of 2 g. or less (Fantus) did not necessarily indicate significant salt depletion. Daily urinary chloride estimations were made on a group of twenty healthy infantrymen 2 weeks after their arrival in Aden. In two the urinary chloride concentration (Fantus) was less than 2 g. on 3 consecutive days, yet neither showed signs of salt depletion or heat illness.

Progress

Oral temperatures fell gradually in all patients and were below 99·0°F within 12 hours of admission in ten of them, in all of whom apparently normal sweating was then observed. None of the patients had been exposed to the risk of malaria. During their hospital admission, which lasted on average 4 days, none developed symptoms or signs suggesting the presence of any infection. When traced 6 weeks later, ten of the patients had remained free of symptoms, one had had an attack of diarrhœa and vomiting a week after his hospital admission, and one had been sent back to England.

Transient Acute Anhidrosis

On several occasions soldiers in Aden reported transient cessation of sweating while working in the sun.

Cpl. C., an intelligent National Service soldier, had arrived by sea from the United Kingdom a month previously and had been doing clerical work in an air-conditioned office in Aden. He was then attached to an infantry platoon prior to selection for a commission. This platoon had also arrived from the United Kingdom by sea a month before, but for 2 weeks it had undertaken graded daily training.

On his 4th day Cpl. C. started his third training exercise, a hard hill climb with the platoon. The environmental temperatures at the camp during the climb were dry-bulb 96°, wet-bulb 82° in the shade, and in the sun the globe thermometer recorded 117°F. The wind speed was 400 ft. per min. and the effective temperature 90·5°F. Near the summit Cpl. C. noticed that his sweating suddenly diminished and he felt unsteady. He stated that he would have fallen if he had been forced to climb higher. On the way down he started to feel cold and noticed that sweating had " stopped completely " all over his body. After reaching the bottom he rested and walked slowly for three-quarters of a mile. He started sweating again slightly. He was examined 20 minutes after the complete cessation of sweating during the descent and his skin was just moist whereas his companions were sweating profusely. His rectal temperature was 101·8°F.

Next day Cpl. C. managed a less severe climb without discomfort, sweating normally throughout. His rectal temperature rose from 99·4 to 100·8°F.

Anhidrosis Following Prickly Heat

Two soldiers who had had generalised prickly heat for several months were admitted to hospital after collapsing during severe exertion. Both said that sudden cessation of sweating had preceded their collapse.

L/Cpl. M. had been in Aden 10 months. Generalised prickly heat had started 4 months after his arrival, and since then he had sweated less than his companions. He played football regularly without discomfort, but on the day of admission he stopped sweating completely in the first few minutes of the game. He developed a headache, became unsteady, left the field, and collapsed outside the M.I. room. On admission to hospital his oral temperature was 100·0°F and his skin was hot, flushed, and dry, apart from scanty sweating over his face. He had widespread mammillaria over his trunk. He noticed that sweating returned while he was lying in bed 10 hours later. Next morning sweating was marked over the face and limbs, and some sweating had returned over the areas with mammillaria, though the mammillaria were hardly less conspicuous than they had been at the time of his admission.

Incidence of Prickly Heat

It seemed possible that acute anhidrosis may sometimes be linked erroneously with preceding prickly heat merely because prickly heat is so common.

A group of twenty-seven Servicemen, living in the same barrack-room, were questioned in November, 1958. Of the twenty men who had been in Aden more than 3 months, sixteen (80%) had had prickly heat and nine (45%) developed mammillaria after exercise. Several had vague symptoms, but only one of them developed sudden anhidrosis and collapsed. In terms of acclimatisation this group was probably similar to that studied by Ladell et al. (1944).

By contrast, out of forty-eight infantrymen selected by taking alternate names from a company roll, only 19% (nine cases) had suffered from prickly heat. These men had arrived in Aden in September and were questioned in December. In the men with prickly heat, improvement took place after 2 weeks and at no time did mammillaria appear on exercise. Only one of the men questioned had developed heat illness (acute anhidrotic heat exhaustion) and at no time had he had prickly heat.

Discussion

To the three categories of anhidrotic heat illness recognised by the M.R.C. committee (1958) this paper adds a fourth, with the following clinical features:

1. The first symptom was sudden diminution or cessation of sweating over almost all the body surface, occurring in partially acclimatised subjects in whom there was no history of prickly heat or other skin disease.
2. This cessation of sweating was noted during or immediately after exertion in severe heat.
3. Though the patients were all incapable of working after sweating stopped, general symptoms were mild. Headache, anorexia, unsteadiness on standing, and mild confusion were the commonest symptoms. No polyuria was reported.
4. On admission to hospital the skin was flushed, hot, and dry, showing no papules, vesicles, desquamation, or mammillaria.
5. The oral temperature on admission did not exceed 102°F. When the patients remained at rest in hospital, at an effective temperature of about 80°F, the condition did not progress to hyperpyrexia or heat stroke, and no evidence of a superadded infection appeared.
6. Sweating appeared normal again in all patients within 2 days, and in most cases within a few hours, of admission to hospital.

The name suggested for this is acute anhidrotic heat exhaustion—reserving chronic anhidrotic heat exhaustion for the condition already described as " attributable to ' chronic ' sweating deficiency, nearly always preceded by severe prickly heat; usually associated with characteristic skin changes. . . . Very slow to return to normal sweating (many weeks)." (Medical Research Council 1958.)

Hearne (1919, 1920) commented on the importance of cessation of sweating as a sign of impending hyperpyrexia. He described one patient with an oral temperature of 100·6°F who reported one evening that sweating had stopped several hours earlier. At 5.30 A.M. next day he was " found in a fully developed attack of heat stroke ". It is likely that this man had the syndrome described in this paper and went on to develop heat stroke because he was exposed to higher temperatures than were usual in Aden.

Ladell, Waterlow, and Hudson (1944) described " borderline hyperpyrexial cases " with defective sweating in which the rectal temperature averaged 104·8°F. Some patients with the Aden syndrome may have belonged to this group, though the average rectal temperature reported by Ladell et al. was considerably higher. Ladell (1957) has suggested that " hyperpyrexia is fundamentally a physiological phenomenon; when the temperature rises, sweating stops and cooling ceases " and has stated elsewhere (Ladell 1958) that " at about 105°F sweating ceases altogether ". As 106°F is the arbitrary lower temperature limit for cases of hyperpyrexia there is for this condition as yet no final answer to the question Leonard Hill asked in 1920: " Is the absence of sweating in heat illness a symptom or a precursor? "

In the Aden cases it is unlikely that the body temperature rose to 105° at the moment when sweating diminished or stopped. If it had, these men would probably not have been able to lose enough heat (by conduction, convection, and radiation) to maintain thermal equilibrium. The probability is that anhidrosis was the primary cause of the heat exhaustion, and not merely a symptom as it may be in cases of hyperpyrexia.

Experimental exposures to heat have so far not produced a sudden diminution of sweating such as these subjects described.

Gerkin and Robinson (1946) showed that in acclimatised men the rate of sweating declined by as much as 80% in 6-hour exposures to a humid environment, whereas in a hot, dry

environment there was little change. Thaysen and Schwartz (1955) confirmed the decline of sweating in acclimatised subjects at rest during 6-hour exposures to intense heat and provided evidence that the decline is due to "secretory" fatigue of sweat-glands. In neither of these experiments was a sudden decline or apparent cessation of sweating observed and the skin was not noted as becoming dry.

Under humid conditions more sweat is produced than can evaporate and sweat-rates may decline considerably before a reduction in evaporative cooling occurs. Adolph (1943), Eichna et al (1945), and Ladell (1955) have all shown that moderate water deficiency has little effect on the sweat-rates of acclimatised subjects.

The physiological mechanism of acute anhidrosis remains obscure; it is not necessarily the same as the one responsible for anhidrosis in cases of hyperpyrexia. Possible causes are a failure of the central mechanism controlling sweating or a failure of the sweat-glands themselves.

Acute anhidrotic heat exhaustion may precede, follow, or be superimposed upon certain other types of heat illness. Under climatic conditions hotter and drier than Aden it is probably much less common as an isolated syndrome, and it may pass unnoticed because sweat evaporates so rapidly that the skin appears dry.

In Aden the only fully acclimatised subjects in whom acute anhidrotic heat exhaustion occurred already had impairment of sweating caused by prickly heat. In these cases, after recovery from the acute episode, a chronic sweating deficiency remained. A possible reason for acute anhidrotic heat exhaustion in these subjects is that exercise induced in them a greater rise of body temperature than in normal people.

Hyperpyrexia, leading to heat stroke, was rare in Aden. One possible reason for this is that at effective temperatures of 80°F a subject at complete rest could probably remain in thermal equilibrium even in the absence of sweating, provided that this was the only abnormality. Another, less likely, explanation is that the sudden cessation of sweating which these patients reported was followed by sweating, which was imperceptible but nevertheless sufficient to control body temperature. In patients who (unlike those described in this paper) develop hyperpyrexia, some additional factor such as extreme exertion, exposure to higher temperatures, or perhaps most likely an occult infection, may cause the temperature to approach 105°F. At this point two effects contribute to the vicious circle:

1. A physiological diminution in sweating, with rising body temperature, in patients in whom sweating was previously normal.

2. A rise in the heat production of the body such that, even in the shade, thermal equilibrium can no longer be achieved without sweating.

Summary

Twelve cases of anhidrotic heat illness of a type which does not seem to have been previously distinguished are reported.

The patients were all incompletely acclimatised soldiers without skin disease affecting the sweat-glands, though two of them had moderate erythema following sunbathing. Sudden diminution or cessation of sweating was noted during or immediately after severe exertion. Sweating was still imperceptible when the patient was admitted to hospital, though the oral temperature was at a range (99–102°F) which might be expected to cause maximal sweating (yet was below that necessary to cause physiological cessation of sweating). Some of the patients were confused and all were drowsy and incapable of further exertion.

The name "acute anhidrotic heat exhaustion" is suggested for this condition.

Recognition of acute anhidrotic heat exhaustion is important because those who develop it may go on to have heat stroke if they are exposed to greater heat stress or further exertion. Early cases offer a valuable opportunity for studying the ætiology and prevention of one of the causes of heat stroke before the picture is complicated by changes secondary to the failure of sweating and the rise of body temperature.

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BIOCHEMICAL EFFECT OF PHENYLACETIC ACID

IN A PATIENT WITH 5-HYDROXYTRYPTOPHAN-SECRETING CARCINOID TUMOUR

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A DISTINCT clinical group of 5-hydroxytryptophan (5-H.T.P.) secreting carcinoid tumours has been described by Sandler and Snow (1958). We record below a further case, previously mentioned briefly (Sandler 1958, 1959), and describe the biochemical effects of phenylacetic acid and phenylalanine. Phenylacetic acid is one of a group of aromatic-acid metabolites of phenylalanine which have been shown by Davison and Sandler (1958) to inhibit 5-H.T.P. decarboxylase in vitro. This enzyme converts 5-H.T.P. to the pharmacologically active 5-hydroxytryptamine (5-H.T.) (Clark et al. 1954).

Case-report

A 76-year-old housewife was admitted for investigation to Joyce Green Hospital in October, 1956, under the care of Mr. J. C. Morris. She had lost weight and had been bleeding from piles for 3 years. At laparotomy, the liver was found riddled with metastases, and a piece was taken for examination. The second part of the duodenum was considered to be enlarged and firmer than normal. No primary tumour was found. Systolic blood-pressure varied from 170 to 200 mm. Hg. She had had no flushing or wheezing attacks, and tended to be constipated. Abnormal heart-sounds were interpreted

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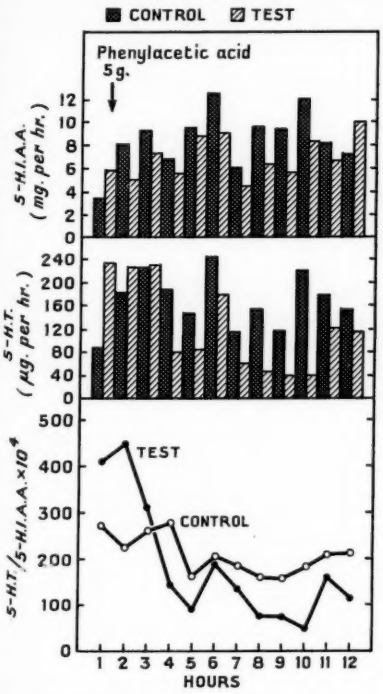

Hourly excretion of 5-hydroxyindoleacetic acid (5-H.I.A.A.) and 5-hydroxytryptamine (5-H.T.) following administration of 5 g. phenylacetic acid by mouth, compared with a control day.

as due to pulmonary stenosis, but the tricuspid valve was considered to be healthy.

In June, 1957, she complained of pains down the thighs, and by the end of 1957 these pains had spread to her back. In January, 1958, she was readmitted to hospital. By now there were signs of both pulmonary and tricuspid stenosis, and there was radiological evidence of metastases in the pelvic bones and vertebræ. No renal metastases were seen in an intravenous pyelogram. No subjective improvement followed trials of phenylalanine and of phenylacetic acid by mouth. When last seen in January, 1959, there was little clinical change.

The piece of liver was examined by Dr. J. C. Burne, who reported that the "section shows solid acinar clusters of fairly regular cells with rounded nuclei and clear cytoplasm. The appearances are consistent with a diagnosis of secondary argentaffin carcinoma (carcinoid). Argentaffin and diazo reactions, negative". Dr. Jacobson of the Strangeways Research Laboratory, Cambridge, found that very few of the cells were argyrophil and confirmed that none were argentaffin.

Further Investigations

Urinary 5-H.T. was estimated by the colorimetric method of Udenfriend et al. (1955b), as modified by Dalgliesh and Dutton (1957), and urinary 5-hydroxyindoleacetic acid (5-H.I.A.A.) by the method of Udenfriend et al. (1955a). Indole chromatography of urine was performed by the method of Jepson (1955). The presence of 5-H.T. on chromatograms was confirmed by the method of Jepson and Stevens (1953); 5-H.T. and other 5-hydroxyindoles were also identified chromatographically by the method of Udenfriend et al. (1955b). The histamine content of the urine was kindly estimated by Dr. G. B. West, using the method of Roberts and Adam (1950).

Successive, accurately timed, hourly specimens of urine were obtained for 12 hours by indwelling catheter on a control day, and again on a "test" day, when 5 g. phenylacetic acid was given by mouth one hour after the investigation had started.

Phenylacetic acid was also given for 5 successive days in a dose of 6 g. daily (2 g. t.d.s.) during which period, and also for the three days preceding and following, 24-hour specimens of urine were obtained.

Neither phenylacetic acid nor its urinary metabolites were found to affect the colour reaction used in the assay procedures.

On another occasion DL-phenylalanine, 30 g. daily (10 g. t.d.s.), was given for 7 days, preceded and followed by 3 control days, and 24-hour specimens of urine collected throughout the 13 days were examined.

Chromatography

5-H.T.P. was present in all specimens in fairly low concentration, and its output appears to have decreased since the patient first came under observation. 5-H.T. and its major metabolite 5-H.I.A.A. were also consistently present. Indolelactic acid appeared in urine specimens passed during the period of phenylalanine administration.

Quantitative 5-hydroxyindole Excretion

When first observed the patient was excreting 106 mg. per 24 hours of 5-H.I.A.A. This has gradually increased over 28 investigations, and recently her output has ranged between 140 and 216 mg. per 24 hours. 5-H.T. excretion has varied between 1·8 and 5·4 mg. per 24 hours.

After administration of a single dose of 5 g. phenylacetic acid by mouth, not only was there a decrease in 5-H.T. and 5-H.I.A.A. excretion, but output of the former tended to be decreased proportionately more than the latter (see figure). This tendency, although less marked, may have been present during continuous treatment with phenylacetic acid, but was not observed during phenylalanine treatment. The red-brown urinary pigment observed in some patients with the carcinoid syndrome (Hanson and Serin 1955, Curzon 1957) was marked in our patient. Its formation appeared to be inhibited during phenylalanine treatment.

Histamine output was 199 µg. per 24 hours, the normal range being 18–62 (Roberts and Adam 1950).

Discussion

The finding of 5-H.T.P. and of greatly increased output of 5-H.T., together with the atypical histological picture and distribution of metastases, indicates that this patient should probably be included in the atypical carcinoid group described by Sandler and Snow (1958).

Smith et al. (1957) thought that the atypical indole excretion pattern in their patient might be produced by renal metastases. An intravenous pyelogram, however, failed to show renal metastases in this woman; moreover, Nelson (1957) has described a patient with a carcinoid syndrome and a urinary excretion of 5-H.T.P. in whom there were no renal metastases at necropsy. When Sandler and Snow (1958) defined this clinical group, they included a patient described by Waldenström et al. (1956), despite the fact that urinary 5-H.T.P. excretion was not mentioned by these authors. Dr. B. Pernow (personal communication) has since found 5-H.T.P. in chromatograms from this patient and in another similar case. The patient described by Heilmeyer and Clotten (1958) is probably a further example of this atypical group.

The absence of flushing attacks and relatively low histamine excretion in our patient, compared with others in this 5-H.T.P.-secreting group, is of interest. Some patients with typical 5-H.T.-secreting carcinoid tumour may also have no flushes during their illness. Evidently other factors exist which determine the tissue response to the humoral agent.

Patients belonging to this atypical group are especially suitable for the biochemical investigation of the effect of 5-H.T.P. decarboxylase inhibitors, as they excrete 5-H.T. directly into the urine—a finding considered by Sandler and Snow (1958) to be an index of direct renal decarboxylation of 5-H.T.P. The finding of large amounts of 5-H.T. in urine secreted following kidney perfusion with 5-H.T.P.

in animals (Sandler and West 1959) supports this hypothesis. Rodnight (1956) had previously suggested that direct renal decarboxylation of 5-H.T.P. might account for some of the small amount of 5-H.T. found in normal urine.

Phenylacetic acid was the most readily available of the group of aromatic acid metabolites of phenylalanine found by Davison and Sandler (1958) to be inhibitory to 5-H.T. decarboxylase in vitro. Because of its relatively low toxicity (Sherwin et al. 1919, Sherwin and Kennard 1919), and in spite of its unpleasant smell, we considered a trial was justified.

The high cost of L-phenylalanine made us use a racemic mixture during a similar trial. The D-isomer is probably not metabolised appreciably in man (Gartler and Tashian 1957). The apparent failure of phenylalanine to affect 5-H.I.A.A. production would suggest that insufficient phenylacetic acid or related compounds were produced from the L-isomer to alter decarboxylase activity.

The appearance of indolelactic acid in the urine during the period of high phenylalanine intake, an observation confirmed by Sandler et al. (1959), is in itself of great interest as this substance is produced in high concentration in phenylketonuria (Armstrong and Robinson 1954) where excess of phenylalanine is also present. The finding may be a consequence of the use of the racemic mixture, however, for Jepson (1958) described high urinary output of indolelactic acid following DL-tryptophan administration, but not when the L-isomer alone was used.

Although it is possible that the decreased 5-H.I.A.A. output observed following phenylacetic acid administration might be due to day-to-day variation, it is difficult to see how the observed reduction in 5-H.T. : 5-H.I.A.A. ratio can also be a coincidence.

Because of relatively high renal blood-flow, it is likely that renal decarboxylase was subjected to a higher concentration of phenylacetic acid than decarboxylase at other sites. The 5-H.T. fraction which passes directly into urine would then show a proportionately greater decrease than that produced outside the kidney. The latter fraction is further metabolised, so that the amount of 5-H.I.A.A. in the urine may thus be considered as an index of extrarenal decarboxylation.

An alternative explanation, which cannot be ruled out, is that following decarboxylase inhibition, 5-H.T.P. might be more readily diverted into another metabolic pathway. One possible pathway would involve oxidation or, more likely, transamination to 5-hydroxyindolepyruvic acid which would then be further metabolised to 5-H.I.A.A. (Blaschko and Hope 1955).

Adaptive enzyme formation either of this postulated aminoacid oxidase or transaminase, or of the decarboxylase itself, may help to explain the apparent decrease in 5-H.T.P. excretion noted in successive urine samples since the patient first came under observation. However, Davison and Sandler (1956) failed to find evidence of adaptive enzyme formation in another enzyme system (monoamine oxidase) which bears an increased load in the carcinoid syndrome.

Further support for the view that phenylalanine metabolites inhibit 5-H.T.P. decarboxylase in vivo has been provided by Pare et al. (1958). They were able to demonstrate decreased decarboxylase activity in phenylketonuria, which may account for the decreased 5-H.T. production observed in this disorder (Pare et al. 1957). Davison et al. (1959) have recently found evidence of such an inhibition in animals treated with phenylacetic acid.

The decrease in 5-H.T.P. output, observed in our patient as her condition progressed, was assessed only roughly from inspection of serial chromatograms, for the comparatively low concentrations in the urine precluded accurate measurements by the method of Udenfriend et al. (1957). For a similar reason, quantitative assay of 5-H.T.P. was not attempted on specimens obtained during drug trials.

Although our patient did not have any of the symptoms usually attributed to excess 5-H.T. production such as flushing or diarrhœa, the biochemical findings following phenylacetic acid were sufficiently suggestive to warrant a trial of this compound in patients with carcinoid syndrome presenting with incapacitating symptoms. Such a trial in patients with 5-H.T.-secreting tumours is described by Sandler et al. (1959).

Summary

In a patient with a 5-hydroxytryptophan-secreting carcinoid tumour, administration of phenylacetic acid appeared to decrease urinary output of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. The findings are compatible with an in-vivo inhibition of 5-hydroxytryptophan decarboxylase.

We are grateful to Mr. J. C. Morris for his kind cooperation in allowing us to investigate his patient; to Miss Lilith Emslie and Miss Doreen Crabtree for skilled technical assistance; and to the Royal Free Hospital Endowment Fund and Roche Products Ltd. for defraying their respective salaries.

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EFFECT OF PHENYLACETIC ACID ON THE CARCINOID SYNDROME

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THE production of 5-hydroxytryptamine (5-H.T., serotonin) by carcinoid tumour has now been well attested. There is considerable evidence to suggest that this amine plays a major part in the pathogenesis of the syndrome associated with a large mass of tumour tissue (for review, see Thorson 1958).

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Although the basic therapeutic problem is that of cancer in general, patients with this particular neoplasm may survive for many years, albeit incapacitated by severe diarrhœa and flushing attacks. It is therefore worth aiming at symptomatic treatment and we present here a new approach.

Most attempts at symptomatic treatment have shared a common rationale—that of finding an antimetabolite to compete with 5-H.T. and block its receptor sites. Many such compounds exist which have marked in-vitro blocking action—e.g., lysergic acid diethylamide (L.S.D.) (Gaddum 1953), brom-L.S.D. (Cerletti and Rothlin 1955), "benzyl analogue of serotonin" (B.A.S.) (Shaw and Woolley 1956)—but these have invariably proved ineffective in treatment (Snow et al. 1955, Goble et al. 1955, 1956, Sjoerdsma et al. 1956, Schneckloth et al. 1957).

Thus a therapeutic impasse has probably been reached, and an alternative line of investigation is needed. One obvious approach would be to attempt to limit the local production of 5-H.T. within the tumour tissue itself. 5-H.T. is elaborated from tryptophan, via 5-hydroxytryptophan (5-H.T.P.) (for biochemical review, see Dalgliesh 1958). As the hydroxylating enzyme has not yet been isolated, any attempt at controlling 5-H.T. synthesis must at present aim at the inhibition of 5-H.T.P. decarboxylase.

Davison and Sandler (1958) recently demonstrated inhibition in vitro by a group of aromatic-acid metabolites of phenylalanine, and Pare et al. (1958) have provided indirect evidence that these compounds may have an in-vivo inhibitory action as well. Sandler and Close (1959) administered one of these metabolites, phenylacetic acid, to a patient with a 5-H.T.P.-secreting carcinoid tumour, and obtained biochemical data which seemed to justify a trial of this relatively non-toxic substance in the carcinoid syndrome. We report here the results of such a trial on five cases of this syndrome.

Case-reports

Case 1.—A 63-year-old male aircraft worker had a 5-year history of diarrhœa. This had gradually become more severe during the past 2 years (6–8 stools per day) and there had often been lower abdominal pain and loud borborygmi. No blood or mucus was present. 6 months before admission he developed swelling of his right ankle, followed 1 month later by similar swelling of his left. At about this time, he noticed the onset of severe flushing attacks, usually confined to face and arms, lasting 2–3 minutes. These could be brought on by emotional disturbance, or by a hot cup of tea, but not by food or alcohol.

He was a red-faced well-built man with a diffuse malar telangiectasia. Typical signs of tricuspid stenosis and incompetence were present, but no involvement of the pulmonary valve was evident. The liver edge was palpated four finger-breadths below the costal margin and was irregular.

Large amounts of 5-hydroxyindoleacetic acid (5-H.I.A.A.) were present in his urine.

Although double-blind studies did not confirm it, the patient was convinced that his diarrhœa was benefited by phenylacetic acid, and he continued to take 4 g. per day as symptomatic treatment up to the time of his death 9 months after admission to hospital.

Case 2.—A 58-year-old housewife had suffered from repeated bouts of colicky abdominal pain since 1948. In 1955 the pain became more severe, occurring 15 minutes after food. She passed 2–3 unformed stools per day.

A central abdominal mass was palpated and on laparotomy this was found to be astride the root of the mesentery. Smaller masses constricted the jejunum in several places. Biopsy was performed and an enteror-enterostomy was carried out to relieve obstruction. Histologically, the tumour tissue was of typical carcinoid variety and the diagnosis was confirmed by the finding of a high urinary 5-H.I.A A. excretion.

After operation, flushing attacks began, which could be brought on by food, hot tea, and emotional disturbance. These have latterly become very severe, lasting 5–10 minutes, are accompanied by loud borborygmi, and are sometimes followed by a patchy cyanosis. Even when not experiencing an episode of flushing, she possesses a high colour with pronounced malar telangiectasia. Apart from a blood-pressure of 240/130, and tachycardia and palpitations during the flushing episodes, there is no cardiovascular abnormality. Despite her central abdominal mass and flushing attacks, she remains tolerably well and there is no diarrhœa at present.

Case 3.—A 56-year-old woman had attacks of pain in the right hypochondrium, backache, loss of weight, and malaise for 1 year. An enlarged liver was felt, and 3 months later at laparotomy this was found to be extensively infiltrated with multiple and small metastases, which were all the same size and looked like sago granules. Although qualitative testing at this time failed to reveal an excess of urinary 5-H.I.A.A., a histological diagnosis of typical malignant carcinoid tumour was made.

After 3 months jaundice gradually supervened, and this deepened during the succeeding 4 months before she was readmitted to hospital. Hepatic fœtor was present and there was gross œdema of the legs and abdominal wall. A rash on her left buttock was thought to be pellagrous. She developed diarrhœa, and an excess of 5-H.I.A.A. was now detected in her urine. A further laparotomy was performed when a primary tumour of small bowel, 3 ft. from the ileocæcal junction, was resected. Her immediate postoperative recovery was satisfactory and allowed a trial of the effect of phenylacetic acid. Clinically this was not helpful, and seemed to cause a mental state similar to alcoholic intoxication. She deteriorated gradually and died 1 month after admission to hospital. Necropsy showed the liver to be replaced largely by tumour nodules, and there were numerous small metastases in the pancreas.

Case 4.—A 47-year-old housewife had an 18-month history of blueness of face and hands, with attacks of facial flushing lasting a few minutes, gradually increasing dyspnœa on exertion with orthopnœa and nocturnal dyspnœa latterly, and ankle swelling. There were frequent attacks of diarrhœa.

She was a plethoric patient with some malar telangiectasia. Pulmonary valvular stenosis and gross tricuspid incompetence were confirmed by cardiac catheterisation. The liver was greatly enlarged and irregular, and there was a palpable mass in the right iliac fossa. A clinical diagnosis of metastatic carcinoid tumour was confirmed by the finding of large amounts of 5-H.I.A.A. in her urine. Congestive cardiac failure developed, which was treated symptomatically.

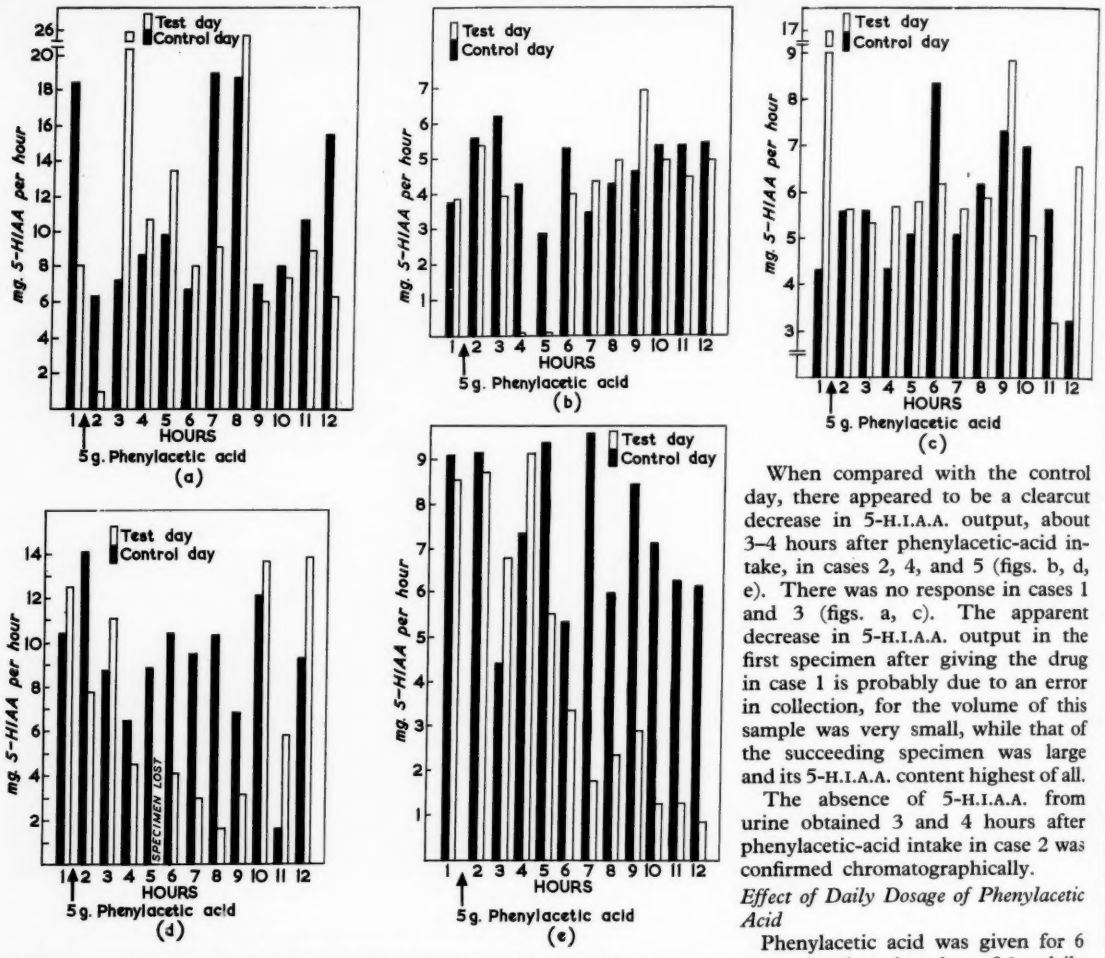
A trial of phenylacetic acid was discontinued because it seemed to cause nausea and vomiting.

Case 5.—A 58-year-old woman presented in 1949 with diarrhœa for which no cause was found on investigation. A year later, this symptom was still present, but a mass could now be felt in the right iliac fossa, and her liver was enlarged. At laparotomy a primary carcinoid tumour was found just proximal to the ileocæcal valve, and metastases were observed in the mesentery of the terminal ileum and the liver.

Several attacks of abdominal pain developed in the following year. No obstructive element was discovered on further laparotomy, but the metastases had increased in size and number.

In 1954, severe flushing attacks developed, which were precipitated by taking food. A year later, large amounts of 5-H.I.A.A. were detected in her urine. She remains tolerably well at present, although the flushes and diarrhœa continue.

The flushes, but not the diarrhœa, appeared to respond dramatically when phenylacetic acid was given, but this observation could not be confirmed during the double-blind studies.



5-H.I.A.A. excretion during test and control days in 5 patients with carcinoid syndrome.

Special Investigations

The effect of phenylacetic acid, and also of phenylalanine which is metabolised to phenylacetic and other aromatic acids which inhibit 5-H.T.P. decarboxylase in vitro, was assessed clinically and biochemically by the following methods:

Urinary 5-hydroxyindoleacetic acid (5-H.I.A.A.), the major metabolite of 5-H.T., was estimated on cases 1, 2, 3, and 4 at the Royal Free Hospital by the method of Udenfriend et al. (1955), and on case 5 at University College Hospital by the method of Macfarlane et al. (1956). The method of Jepson (1955) was used for indole chromatography of urine.

Phenylacetic acid, phenylalanine, and their urinary metabolites did not alter the 5-H.I.A.A. extraction and colour reaction. Characteristic urinary 24-hour 5-H.I.A.A. output and chromatographic pattern in the 5 patients prior to treatment is shown in the table.

Effect of Phenylacetic Acid on Hourly 5-H.I.A.A. Excretion

In all patients, successive, accurately timed, hourly specimens of urine were obtained for 12 hours by indwelling catheter on a control day, and on a " test " day, which followed the control day in cases 1–4, and preceded it in case 5. Placebo, or 5 g. of phenylacetic acid, was given after the first hour.

When compared with the control day, there appeared to be a clearcut decrease in 5-H.I.A.A. output, about 3–4 hours after phenylacetic-acid intake, in cases 2, 4, and 5 (figs. b, d, e). There was no response in cases 1 and 3 (figs. a, c). The apparent decrease in 5-H.I.A.A. output in the first specimen after giving the drug in case 1 is probably due to an error in collection, for the volume of this sample was very small, while that of the succeeding specimen was large and its 5-H.I.A.A. content highest of all.

The absence of 5-H.I.A.A. from urine obtained 3 and 4 hours after phenylacetic-acid intake in case 2 was confirmed chromatographically.

Effect of Daily Dosage of Phenylacetic Acid

Phenylacetic acid was given for 6 successive days, in a dose of 6 g. daily (2 g. t.d.s.), in cases 1 and 2, during which period and also for the preceding and subsequent 3 days, 24-hour specimens of urine were obtained. In case 5, phenylacetic acid was given for 9 days in a dose starting at 2·5 g. daily and gradually increasing to 5 g. daily. 24-hour urine specimens were collected during this period, and also for 5 days before and 2 days after. The drug was stopped after 3 days in case 3 because of toxic signs.

URINARY CHROMATOGRAPHY IN FIVE PATIENTS BEFORE TREATMENT

Patient	5-H.I.A.A. (mg. per 24 hr.)	Chromatographic pattern
1	78–204	Typical carcinoid
2	68–117	" "
3	126	Excess indolelactic acid and 5-H.I.A.A.
4	532	Typical carcinoid
5	75–180	" "

There was no difference in 5-H.I.A.A. output between test and control days. Analyses were not attempted on case 3 because the patient was partially incontinent. Case 1 considered that his diarrhœa was much less troublesome, although his flushes were not affected. Case 5 stated that her flushing attacks were less frequent, but that there was no alteration of her diarrhœa.

Effect of Daily Dosage of DL-phenylalanine

DL-phenylalanine, 30 g. daily (10 g. t.d.s.), was also given to cases 1 and 2 with similar control and " test " periods, during which 24-hour specimens of urine were also collected.

No difference between 5-H.I.A.A. output on test and control days was apparent in this investigation either. Large amounts of indolelactic acid, demonstrated chromatographically, were evident in urine passed during phenylalanine intake. This finding was not present in urine passed on control days. There was no effect on either flushing attacks or diarrhœa.

On the 4th evening of treatment, case 1 became mentally confused. This coincided with a dose of chlorpromazine which he had been given as a sedative. By the following day he was well orientated and continued the course without further trouble.

Clinical Trial of Phenylacetic Acid

Phenylacetic acid or placebo, 6 g. daily (2 g. t.d.s.), were allocated at random on 14 successive days in patients 1, 2, and 5 to make a total of 7 days of each treatment. Neither the patient nor the medical officer knew which treatment was being given on a particular day. Patients were provided with questionnaires, and, amongst the information they were asked to record, was the number and time of flushes and their severity, and the number of stools per day.

Each flushing attack was scored 1, 2, or 3, according to the patients' description of it as mild, moderate, or severe respectively. Mean scores for treatment days were compared with those on which placebo was taken, in each of the 3 patients.

In no case was there a significant difference between phenylacetic-acid therapy and placebo. The mean number of stools on treatment days were similarly compared with those on control days in each patient. There was, likewise, no significant difference.

Discussion

The decrease in 5-H.I.A.A. excretion, in 3 out of 5 patients with the carcinoid syndrome in response to acute challenge with phenylacetic acid tends to confirm the conclusion of Sandler and Close (1959) that 5-H.T.P. decarboxylase is inhibited in vivo as well as in vitro. Davison et al. (1959) have recently produced evidence in animals to confirm this. The finding could not be confirmed for 24-hour excretion values in the one patient, out of the two treated with daily phenylacetic acid, in whom a decrease in 5-H.I.A.A. output was obtained in response to acute dosage. This is not surprising, for any small and temporary change in 5-H.I.A.A. excretion would probably be obscured by the large pool and its day-to-day fluctuation. If 5-H.T.P. also follows an alternative metabolic pathway to 5-H.I.A.A., as postulated by Sandler and Close (1959), any decrease in 5-H.I.A.A. output would be minimal, and would not then be a satisfactory index of the degree of decarboxylation.

Although at first cases 1 and 5 suggested that there was some alleviation of diarrhœa and flushing respectively, this could not be confirmed when treatment was given on a double-blind basis. Although the design of this particular experiment did not rule out the possibility of a cumulative effect of daily consecutive dosage, it is more likely that phenylacetic acid is an insufficiently active inhibitor of 5-H.T.P. decarboxylase in the patient with the carcinoid syndrome. Inhibition may fail for a variety of reasons—too rapid conjugation and excretion, impermeability of tumour tissue, development of tolerance—but we do not have enough data to decide which at present.

Despite the failure to demonstrate any objective evidence of clinical improvement, case 1 was convinced that his diarrhœa was less severe when he was taking his tablets. He persisted with these, in fact, until his death.

If phenylacetic acid is active in man in vivo, it might be expected, when given by mouth, to inhibit 5-H.T.P. decarboxylase in the argentaffin cells in the gut, which are anatomically easily accessible. Any agent which interferes with the local production of 5-H.T. by these cells might be expected to decrease gut motility; for Bülbring and Lin (1958) have shown that 5-H.T. may play a part in the maintenance of normal gut motility. The large mass of tumour tissue in carcinoid disease—which may, however, be inaccessible to an inhibitor such as phenylacetic acid—may be a reservoir of a continuous output of humoral agent passing to the gut to stimulate it, despite any inhibition of locally produced 5-H.T. Kowlessar et al. (1958) have detected an excess of 5-H.I.A.A. in the urine of patients with tropical sprue. We would suggest that phenylacetic acid may prove to be a valuable supplementary treatment for severe diarrhœa associated with this condition, where any excess of 5-H.T. is presumably elaborated locally in the gut.

A relation between 5-H.T. and carcinoid flushes is probably more complex. Smith et al. (1957) and Rotbart (1958) have demonstrated an increased skin sensitivity to 5-H.T. in patients with carcinoid tumour who have flushing attacks. The severity of the attacks may bear little relationship to amine production.

Sandler (1959) suggests that a " constitutional predisposition " may be a factor in the pathogenesis of these flushes. He has observed a middle-aged patient with carcinoid syndrome who had " typical " flushing attacks despite a 5-H.I.A.A. output of less than 30 mg. per 24 hours. She had tended to flush easily since adolescence. He also described a young girl with typical flushing attacks, who had had a solitary carcinoid tumour of appendix removed a few months previously. She had a persistently normal 5-H.I.A.A. output. Any apparent response of flushing attacks to phenylacetic acid in case 5 must, therefore, be viewed in this light. It is well known by those with much experience of the syndrome that flushes can easily be precipitated by emotional factors.

No response to treatment can be expected in the established acquired heart lesions. An instructive case, which illustrates this point, was described by Thorson et al. (1958). When carcinoid tumour tissue, which was encapsulated in a dermoid cyst of ovary, was completely extirpated, flushes, and diarrhœa disappeared, but the heart-valve lesions remained.

If the clinical response to phenylacetic acid in our patients was, at best, marginal, that to DL-phenylalanine was unequivocally negative, presumably because of insufficient production of the various aromatic-acid inhibitors. The observation of indolelactic acid in urine specimens obtained during this treatment is in line with the finding of Sandler and Close (1959). The probable toxic reaction to chlorpromazine in case 1 perhaps justifies some caution in the use of this drug in conjunction with the group of compounds considered here.

Of the group of aromatic-acid metabolites of phenylalanine shown by Davison and Sandler (1958) to have an in-vitro inhibitory action on 5-H.T.P. decarboxylase, phenylacetic acid was chosen for further investigation in

the carcinoid syndrome for several reasons: it is known to have relatively low toxicity (Sherwin and Kennard 1919, Sherwin et al. 1919); it is stable; it is cheap. An unpleasant odour is its main disadvantage, but this did not appear to trouble our patients.

Most of this compound is conjugated with glutamine in the liver, and the phenylacetylglutamine thus formed is excreted in the urine (Salkowski and Salkowski 1879). It is probably relevant that the only toxic response to phenylacetic acid was in case 3, in which severe liver failure developed. Another unusual feature of case 3 was the high concentration of indolelactic acid in the pretreatment urine. Armstrong et al. (1958), however, noted an increased output of indolelactic acid in patients with (unspecified) liver disease.

It is of interest that toxic manifestations so far described refer to the central nervous system, for in the brain, enzymes which have been shown to be sensitive to phenylacetic acid are present in high concentration. (Fellman 1956, Davison and Sandler 1958, Hanson 1958). Phenylacetic acid or related compounds may thus prove to be important research tools in the investigation of central nervous system function. It probably follows, however, that related compounds which prove to be more efficient inhibitors of 5-H.T.P. decarboxylase must be impermeable to the blood-brain barrier if they are to be of use in combating the symptoms of the carcinoid syndrome.

Summary

The administration of phenylacetic acid to 5 patients with carcinoid syndrome resulted in a decreased output of 5-hydroxyindoleacetic acid in 3 of them. This finding is compatible with an in-vivo inhibition of 5-hydroxytryptophan decarboxylase by phenylacetic acid. There was no symptomatic relief of flushing attacks or of diarrhœa.

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FIVE CASES OF SICKLE-CELL HÆMOGLOBIN-C DISEASE

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THE purpose of this paper is to present five cases of sickle-cell hæmoglobin-C disease all diagnosed within eighteen months in an East End Hospital. This condition is a cause of anæmia and bizarre symptoms notably during pregnancy. It is a heterozygous state resulting from the inheritance of two abnormal alleles, one for hæmoglobin S and one for hæmoglobin C; it runs a relatively benign course but under conditions of stress it may give rise to crises closely resembling those of sickle-cell anæmia. It was first described in the United States in 1950 by Itano and Neel and then from Africa in 1954 by Edington and Lehmann; but so far there has been only one recorded case in this country (Bannerman and White 1957).

Case-reports

Case 1.—A Jamaican woman, aged 38. For her first pregnancy she attended another hospital where she was diagnosed as a case of megaloblastic anæmia. She failed, however, to respond to folic acid or vitamin B_{12} (cyanocobalamin). She developed severe pre-eclampsia for which cæsarean section was performed (January, 1957), with delivery of a living child. She had a stormy convalescence with pulmonary infection and breakdown of her abdominal wound; but she was discharged fit with a hæmoglobin of 10·7 g. per 100 ml.

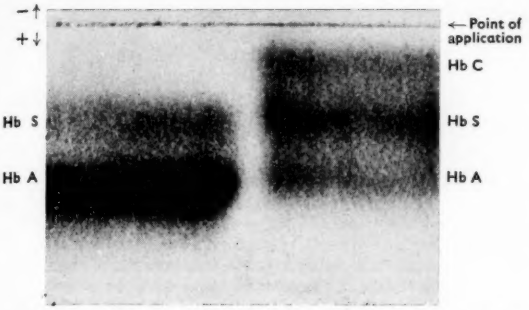
She first attended Hackney Hospital for her second pregnancy in October, 1957, at the twenty-second week of pregnancy, when her hæmoglobin was 8·3 g. per 100 ml. It dropped to 5·7 g. by December; and she was therefore admitted. After a transfusion of four pints of blood her hæmoglobin rose to 8·2 g., but she started to complain of abdominal pain for which no cause could be found and developed pyrexia and a productive cough with bloodstained sputum. Her hæmoglobin fell to 5·2 g. and further hæmatological investigation showed a reticulocyte-count of 6%, sickling of the red cells at reduced oxygen tension, many target cells in the Leishman-stained blood-film, and reduced osmotic fragility of the red cells. Paper electrophoresis of the hæmoglobin showed equal proportions of hæmoglobin S and hæmoglobin C, with a small amount of hæmoglobin A, the last derived from the transfused blood. After another two pints of blood she slowly improved. Because of severe contracted pelvis she had a cæsarean section on Jan. 20, and was delivered of a healthy infant. She discharged herself on the third day after delivery and a follow-up was not possible.

Case 2.—A 23-year-old Nigerian woman had a miscarriage at four months in 1956. She first attended this hospital in June, 1958, when seventeen weeks pregnant. Her hæmoglobin was 10·7 g. per 100 ml.; and she complained of recurrent abdominal pain which was attributed to constipation. Her hæmoglobin fell to 9·6 g. by October; and further hæmatological investigation revealed many target cells in the peripheral blood-film, sickling of the erythrocytes at reduced oxygen tension, and a decreased osmotic fragility. Electrophoresis of the hæmoglobin showed hæmoglobin S and hæmoglobin C in equal proportions. She was delivered normally of a living infant and had an uneventful puerperium.

She remains well; and her hæmoglobin is 11·1 g. per 100 ml.

Case 3.—A Jamaican woman aged 36 first attended here for her eighth pregnancy in January, 1957. At that time her hæmoglobin was 10·4 g. per 100 ml.; and a macrocytic anæmia was suspected but not proved. There was no history of anæmia or of any other trouble with any of her previous pregnancies in Jamaica. She had a normal delivery and puerperium.

She attended again in August, 1958, for her ninth pregnancy when twenty-four weeks pregnant. Her hæmoglobin was 10·4 g. She was admitted on Dec. 7, 1958, with premature



Hanging-strip paper electrophoresis at pH 8·6 of (left) a hæmoglobin A-S sample, and (right) of hæmoglobin from case 3. This patient had received a blood-transfusion before electrophoresis and therefore shows hæmoglobins S, C, and A.

rupture of membranes and was delivered normally on Dec. 10 of a living infant. Two hours after delivery she collapsed with hæmorrhage from a cervical tear; blood and plasma were given and the tear was repaired. During labour she had pyrexia; and she complained of pain in the left hip and thigh. She had no abnormal physical signs in that region and the X-ray appearances were normal. The pyrexia persisted; and on Dec. 12, when she complained of pain behind the sternum and in the epigastrium, an acute abdominal condition was suspected. On Dec. 16 she had a rigor, and septicæmia was considered a possible diagnosis. At this stage her hæmoglobin was 7·4 g. per 100 ml. and further hæmatological investigation showed 4·5% reticulocytes, many target cells in the peripheral blood-film, sickling of the red cells at reduced oxygen tension, and reduced osmotic fragility. The electrophoresis confirmed that this was another case of sickle-cell hæmoglobin-C disease. A further two pints of blood was given. The pyrexia and pain in the hip continued until Jan. 6, though no cause was found on clinical or radiological examination. The pain then ceased and the temperature returned to normal.

Apart from tiredness she now has no symptoms and her hæmoglobin is 10·1 g. per 100 ml.

Case 4.—A Jamaican woman aged 24 first attended this hospital in October, 1958, nineteen weeks pregnant. She gave a history of three normal deliveries in Jamaica. Her hæmoglobin was 10·9 g. per 100 ml. In February, 1959, she was admitted because of pain in the chest for two weeks and because "she felt as if she had flu". There were abnormal physical signs in the chest but the X-ray was normal and a diagnosis of virus pneumonia was made. She was discharged after ten days' rest without chemotherapy, feeling well. Four weeks later her hæmoglobin was 9·6 g. and a peripheral blood-film showed many target cells. She failed to attend again until April 24 when she was admitted complaining of pain in the left elbow and both knees. She had no abnormal physical signs in the joints but hæmatological examination revealed sickling of the red cells, 2% reticulocytes, and decreased osmotic fragility. Sickle-cell hæmoglobin-C disease was confirmed by electrophoresis. She was delivered on April 25 of a living infant, and apart from minor aches in the knees and elbows had an uneventful puerperium.

Case 5.—A 38-year-old Jamaican was admitted to this hospital in May, 1959, with pain in his leg and slight pyrexia. A provisional diagnosis of sciatica with the differential diagnosis of osteomyelitis was made. His hæmoglobin was 12·4 g. per 100 ml. and a peripheral blood-film showed that almost all his red cells were target cells. Further examination revealed 1% reticulocytes, sickling of the erythrocytes, and decreased osmotic fragility. Electrophoresis of the hæmoglobins confirmed that this was another case of sickle-cell hæmoglobin-C disease. His leg pain was ascribed to this: it subsided with rest and the patient was discharged symptom-free after a week.

Discussion

The five patients had certain features in common. They were coloured; none gave a history suggestive of sickle-cell anæmia; and all showed anæmia varying from mild to severe, sickling of the erythrocytes at reduced oxygen tension, many target cells in the peripheral blood-film, and decreased osmotic fragility of the red cells.

Each case presented differently. Case 1 presented as a severe anæmia late in pregnancy with sickle-cell crises just before delivery; case 2 as a mild anæmia during pregnancy; case 3 with sickle-cell crises during labour and in the puerperium; case 4 with sickle-cell crises just before delivery; and case 5 as an atypical sciatica.

The differential diagnosis was sickle-cell trait, sickle-cell anæmia, and the heterozygous condition of sickle-cell disease with another abnormal hæmoglobin or with thalassæmia. The abnormal red-cell fragility and the numerous target cells made sickle-cell trait unlikely; and sickle-cell anæmia was improbable in the absence of the typical habitus and of the previous clinical episodes so characteristic of this disease. Electrophoresis of the hæmoglobin confirmed that all 5 cases were examples of sickle-cell hæmoglobin-C disease. In cases 2, 4, and 5 a hæmoglobinopathy was initially suspected because of the large number of target cells in the peripheral blood-film. These suggest the presence of hæmoglobin C: they appear in large numbers in C-trait carriers and are a characteristic feature of homozygous hæmoglobin-C disease.

The pathology of sickle-cell hæmoglobin-C disease in the adult has been likened to that of sickle-cell anæmia in the child (Edington 1957). Sickle-cell anæmia has been called the great masquerader (Winsor and Burch 1945); and the symptoms of sickle-cell hæmoglobin-C disease can vary from none to sudden death in a crisis (Edington 1957). The term sickle-cell crisis has been defined by Smith and Conley (1954) as episodes of pain, fever, and other features which occur in association with sickling, whether or not associated with increased blood-destruction. Crises are caused by the blocking of small vessels by impacted masses of sickle cells, giving rise to thrombosis and infarction. It is not known why this happens; but it has been suggested (Edington and Lehmann 1954) that in conditions of relative anoxæmia, and particularly in pregnancy, intravascular sickling occurs even when the condition is not classical homozygous sickle-cell anæmia.

All 4 female patients were pregnant at the time of diagnosis and all authors (Smith and Conley 1954, Bannerman and White 1957, Edington 1957) agree that pregnancy may have an adverse effect on sickle-cell hæmoglobin-C disease. The mortality from it during pregnancy is said to be very high (Smith and Conley 1954, Edington 1957). It is interesting that case 3 had survived seven pregnancies and case 4 three pregnancies without any apparent harm.

Lehmann (1959) has described the ethnological distribution of the abnormal hæmoglobins throughout the world: with very few exceptions, hæmoglobin S and hæmoglobin C occur only in the Negro races. With the large movements of population, particularly the influx of West Indians into this island, many more cases will probably be diagnosed here. At Hackney Hospital in the past two years there have been, in addition to sickle-cell trait carriers, 1 case of sickle-cell thalassæmia and 1 case of sickle-cell anæmia, as well as the 5 cases of sickle-cell hæmoglobin-C disease described above.

There is no specific treatment for sickle-cell hæmo-

globin-C disease, although acetazolamide has been reported to reduce the incidence of sickling in sickle-cell anæmia (Hilkovitz 1957). Control of infection with antibiotics, good food, hæmatinics, and blood-transfusions where indicated, with a high standard of obstetric care, would seem to be the only treatment. Special care is also required if anæsthesia should be necessary because of the risk of anoxia.

Summary

Five cases of sickle-cell hæmoglobin-C disease, seen in the East End of London, are described, and the diagnostic features discussed. The diagnosis can be made on clinical grounds with the aid of simple hæmatological techniques. One should consider the hæmoglobinopathies in any coloured person with anæmia or with vague symptoms, notably joint pains.

As sickle-cell hæmoglobin-C disease is a particular hazard in pregnancy, routine examination of a blood-film for target cells in all pregnant coloured patients is recommended.

I should like to thank Miss Gladys Dodds, gynæcologist to Hackney Hospital, for permission to publish the first 4 cases who were admitted under her care; Mr. M. F. Pilcher, orthopædic surgeon to Hackney Hospital, for permission to publish the fifth case; and Dr. Hermann Lehmann, of St. Bartholomew's Hospital, London, who carried out the electrophoreses and who has given much helpful advice and encouragement.

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INHIBITION BY INTERFERON OF THE GROWTH OF VACCINIA VIRUS IN THE RABBIT SKIN

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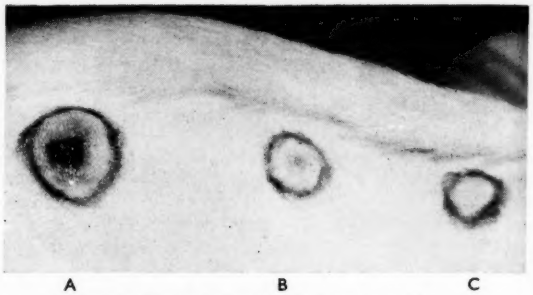
INTERFERON is the name of a substance with many of the properties of a wide-spectrum viral antibiotic, which was found during the study of the virus interference phenomenon (Isaacs and Lindenmann 1957). Among its interesting properties are that it is a protein of low toxicity to tissues and that it is apparently non-antigenic (Burke and Isaacs 1959) and able to inhibit the growth of a large variety of viruses. Thus interferon prepared by incubating chick-embryo cells with inactivated influenza virus can inhibit the growth in tissue culture of the small-sized encephalitis viruses, medium-sized viruses such as the influenza viruses, and large viruses like those of the pox group.

Earlier, we reported that interferon inhibited the growth of vaccinia virus in the rabbit skin (Lindenmann, Burke, and Isaacs 1957); but, although this result was found in a number of experiments, in other cases preparations of interferon which were shown to be active in tissue culture gave little or no protection when tested in the rabbit skin.

It had been found earlier that inactivated influenza virus interfered with the growth of vaccinia virus in the rabbit skin (Depoux and Isaacs 1954), and, since this interference effect was thought to be mediated through interferon, the variable results obtained with interferon seemed to be inconsistent with this hypothesis. The inconsistency was heightened when it was found that inactive influenza virus, tested at the same time as interferon, regularly protected rabbits against vaccinial infection. One explanation which was considered was that when inactive influenza virus was injected into the rabbit skin it produced interferon *locally*, and that this "rabbit-skin" interferon was more effective than interferon prepared in chick cells. This suggestion seemed to be more likely in the light of experiments carried out quite independently by Tyrrell (1959). Tyrrell found that interferon prepared in chick cells was much more active when it was tested in chick cells than when it was tested in calf cells, and the converse was equally true.



A B C

Lesions produced by vaccinia virus in the rabbit skin.

Site A was inoculated intradermally with 0·1 ml. buffered salt solution, site B with 0·1 ml. of an interferon preparation diluted 1/3, and site C with 0·1 ml. of undiluted interferon. All three sites were ringed with indelible pencil. 24 hours later all three sites were inoculated with 100,000 infective doses of vaccinia virus in an 0·1 ml. inoculum. The photograph was taken 5 days later.

It therefore seemed worth while to prepare some interferon in rabbit cells and test its action in the rabbit skin.

Investigation

Preparation of Interferon

Tissue cultures were set up from trypsinised, finely minced rabbit kidneys. The cells were grown in 8-ounce bottles in a medium containing 10% rabbit serum and 90% Parker 199 medium. When satisfactory cultures were obtained the medium was replaced by 199 medium in which 2000–4000 agglutinating doses of ultraviolet-irradiated influenza virus (strain MEL) were incorporated. This was left in contact with the cells for two to three hours at 37°C and the cells were then washed and incubated overnight at 37°C with fresh 199 medium. This fluid was then removed and was used as the source of interferon. In some experiments, more 199 medium was added and the interferon was harvested after a further twenty-four hours. In other experiments the cells were kept in 199 medium plus rabbit serum for a further week, when they were again treated with ultraviolet inactivated influenza virus. In this way the same cells could be repeatedly used to produce new "crops" of interferon.

The interferon was concentrated 3–10-fold by dialysis against polyethylene glycol ('Carbowax' 20M). Part of each preparation was also dialysed overnight at 2°C against buffer at pH 2 and then overnight against buffer at pH 7. Interferon is known to be stable under these conditions whereas the influenza virus is rapidly destroyed at pH 2 (Lindenmann et al. 1957).

Experiments in the Rabbit Skin

The rabbits' skins were closely clipped with an electric clipper and the interferon preparations were then inoculated intradermally in 0·1 ml. volumes. The inoculated areas were marked with indelible pencil. Control areas were inoculated with the same volume of buffer. Next day all sites were inoculated with a standard dose of vaccinia virus taken from a stock kept in capillary tubes at −78°C. Usually about 100,000 infective doses of vaccinia virus were used. Readings were made when the control lesions were maximal—i.e., on the fifth day after the virus was inoculated. When smaller doses of vaccinia virus were used readings were made later.

The results of a representative experiment are shown in the figure. Site A is the control site. Site B shows the effect of a 10-fold concentrated interferon preparation diluted 1/3; the vaccinial lesion is greatly reduced in size compared with the control. Site C shows the effect of the same preparation of interferon tested undiluted; the vaccinial lesion is completely suppressed. Readings taken at later dates (up to three weeks) showed the same picture and there was no tendency for lesions to develop late in interferon-treated sites.

Tissue-culture cells which had produced one " crop " of interferon appeared to be quite healthy when they were examined in the microscope; after one week's interval therefore they were again stimulated with inactive virus to see whether they would produce more interferon. It was found that 2nd and 3rd " crops " of interferon could be harvested from the same culture of cells, and it seems that these cells can be repeatedly stimulated to produce interferon. Unconcentrated fluids of all three crops did not give significant protection, however, and concentration by a factor of about 3-fold was necessary to obtain some protection. It was also shown that the protective effect of the interferon was stable after treatment at pH 2, as was found with interferon prepared in chick cells (Lindenmann et al. 1957).

Interferon Given at Different Times

In the above experiments interferon was given the day before the virus in order that it could exert its maximal protective action (Lindenmann et al. 1957). In another set of experiments the interferon was given (*a*) the day before the vaccinia virus, (*b*) mixed with it, or (*c*) the day after it. In these experiments, the time at which protection was found depended on the dose of vaccinia virus that was used.

With 10,000–100,000 infective doses of vaccinia virus, complete protection was found when the dose of interferon used was given the day before the virus, but not along with or after the virus. With smaller doses of vaccinia virus—i.e., 10–1000 infective doses—complete protection was found when the same dose of interferon was given the day before, or along with, the challenge virus, but not when it was given the day after. Further experiments are contemplated with more concentrated preparations of interferon to see whether protection against small doses of virus can be obtained when the interferon is injected after the virus.

Specificity of Interferon

To see whether the effectiveness of the interferon prepared in rabbit cells was due to the cellular specificity factor (Tyrrell 1959) some experiments were carried out in collaboration with our colleague Dr. J. S. Porterfield, using the plate technique which he has developed (Porterfield 1959). Interferon prepared in rabbit and chick cells was tested by the plate method with chick-embryo cells and vaccinia virus. We found that interferon prepared in chick cells gave good zones of protection, whereas interferon prepared n rabbit cells gave no protection. This is just the reverse of what happened when the same preparations of interferon were tested in rabbits; in this case the interferon prepared in chick cells gave slight protection whereas the interferon prepared in rabbit cells gave complete protection. It is clear, therefore, that the specificity effect described by Tyrrell applies also to the present system.

Discussion

Interferon is known to inhibit the multiplication of many different viruses in vitro, and it also protects cells from the cytopathic action of a number of viruses. This is most readily visualised in fig. 1 of the accompanying paper by Porterfield (1959) where it can be seen that a zone of cells protected from virus action is formed round the interferon in the central cup. These in-vitro effects have now been shown to apply to one in-vivo infection, and, since the protected sites in the rabbit skin showed no macroscopic abnormality, it appears that interferon can inhibit virus growth at concentrations which do not show any obvious toxic effects.

The fact that interferon prepared in rabbit cells was much more active in the rabbit skin than interferon prepared in chick cells is clearly another example of the cellular specificity effect described by Tyrrell (1959). This could be explained by postulating that cells take up homologous protein more readily than heterologous protein; an example of this comes from the work of Halliday (1955) and Bangham and Terry (1957) who showed that the gut of the suckling rat absorbed homologous antibody much more readily than heterologous antibody given by mouth. Whether or not this type of effect explains the cellular specificity shown by interferon, the subject requires more investigation since it would have obvious practical importance in any attempt to use interferon to treat viral infections in vivo. Another practical point from these experiments is that rabbit-kidney cells continued to be able to produce interferon for at least two to three weeks. Experiments are now in progress to see how long cells can be maintained in this state.

It was known from experiments carried out in vitro that some hours were required before the inhibitory action of interferon was fully established (Lindenmann et al. 1957). Hence it was not surprising to find that interferon did not protect against a large dose of vaccinia virus unless it was given before the virus. With smaller doses of virus, protection was found when virus and interferon were given together; presumably under these conditions the interferon protected enough cells to prevent the development of a vaccinial lesion, although it probably did not prevent the first cycle of multiplication of the virus originally inoculated. So far it has not been possible to achieve protection when the interferon was given the day after the virus, but there seems to be no theoretical reason why this could not be achieved if large enough doses of interferon were used and there were sufficient uninfected cells present to protect. This possibility is now being investigated experimentally. Also the use of more than one dose of interferon seems to merit investigation, since evidence from experiments with West Nile virus grown in tissue culture (Isaacs and Westwood, in preparation) suggests that cells that are not dividing are protected for at least ten days by a single inoculation of interferon, whereas the effect of a single dose of interferon seems to pass off much more rapidly when the cells are able to divide.

Summary

Interferon prepared in rabbit kidney cells was found to protect rabbits against intradermal infection with vaccinia virus. With large doses of virus, protection was complete when the interferon was given the day before the virus. With smaller doses of virus, protection was obtained when the interferon was given before, or along with the virus. When tested in the rabbit skin, interferon prepared in chick cells was much less effective than interferon prepared in rabbit cells; when the same preparations were tested in chick cells in vitro the converse was found.

We should like to thank Mr. V. G. Law for his able technical help.

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A SIMPLE PLAQUE INHIBITION TEST FOR ANTIVIRAL AGENTS: APPLICATION TO ASSAY OF INTERFERON

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THE diffusion of an antibacterial agent through agar to produce a zone of inhibition of bacterial growth was first applied to the assay of penicillin in the Oxford cup method (Abraham et al. 1941). The technique was modified and extended by Humphrey and Lightbown (1952) who considered the theoretical aspects of the system. The development of a plaque technique for animal viruses by Dulbecco (1952) raised the possibility that antiviral agents might be similarly assayed with virus plaques replacing bacterial colonies. The technique to be described was devised for use with yellow fever virus and yellow fever immune sera. Details of this study will be presented elsewhere. The antiviral effect of interferon (Isaacs and Lindenmann 1957) has been demonstrated by the present technique against a wide range of viruses and the method may also be used to assay the concentration of a preparation of interferon.

Materials and Methods

A suspension of living cells in a nutrient medium is incubated overnight at 37°C. The following morning the cells have become attached firmly to the glass and the medium is withdrawn. The cell sheet is flooded with an appropriate dilution of virus and the plates are incubated for two hours to allow virus to infect the cells. The residual inoculum is removed and the cell sheet is covered with a layer of agar incorporating cell nutrients and a vital stain, neutral red. This is included to distinguish between living cells, which take up the dye, and dead cells, which do not. After half an hour at bench temperature to allow the agar to harden, fish-spine beads dipped in interferon are placed on the surface of the agar.

Upon incubation two processes take place concurrently. Interferon from the bead diffuses through the agar and virus multiplies in infected cells and is released to infect contiguous uninfected cells. If the cells have been exposed to concentrations of interferon above a minimal critical level, virus multiplication is blocked and the cells remain healthy and retain the neutral red stain. Where the concentration of interferon is below the critical level, virus enters fresh cells to undergo further cycles of multiplication which then proceed to plaque formation. The effect of interferon is seen as a zone surviving cells surrounding the central bead in which plaque production has been inhibited (see figs. 1 and 2).

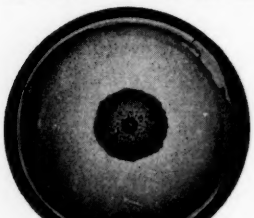

Fig. 1.

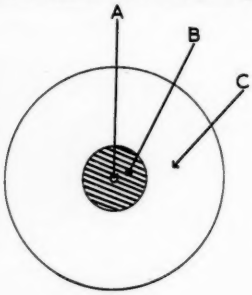

Fig. 2.

Fig. 1—Photograph of a culture infected with 60,000 plaque-forming units of Bunyamwera virus and treated with a bead filled with interferon.

Fig. 2—Diagrammatic representation of fig. 1.
A, fish-spine bead filled with interferon.
B, zone of protected cells, stained with neutral red, in which plaque formation is inhibited.
C, area of confluent plaques in which all the cells have been destroyed and have lost the neutral red stain.

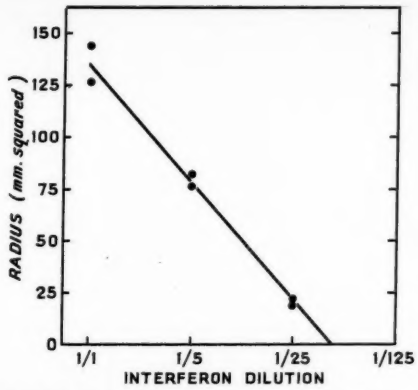

Fig. 3—Graph shows the linear relationship between the area of the zone of inhibition (plotted as radius in mm. squared) against the dilution of interferon on a logarithmic scale.

Cell Suspensions

These are prepared from 10-day-old chick embryos by the Dulbecco technique with modifications described elsewhere (Porterfield 1959, Porterfield and Allison 1959). The final suspension is adjusted to contain 8–10 million cells per ml. Flat-bottomed borosilicate glass petri dishes 60 mm. in diameter receive 8 ml. of suspension each. The growth medium and the overlay medium are both buffered with tris (hydroxymethyl) aminomethane so that the entire incubation can be carried out in a conventional laboratory incubator without the need for a continuous flow of carbon dioxide.

Arthropod-borne Viruses

Yellow fever (French neurotropic strain), West Nile (Egypt 101 strain), Bunyamwera (Smithburn et al. 1946), and Western equine encephalomyelitis viruses were kept as 10% suspensions of infected mouse brain in 10% calf serum in saline.

Vaccinia virus and influenza virus (MEL strain) were standard egg-grown strains. All virus stocks were stored in sealed glass capillary tubes frozen at −70°C.

Interferon

A batch prepared in chick-embryo cells and a batch prepared in rabbit cells were used in all experiments. These are the same stocks of interferon as those referred to by Isaacs and Westwood (1959a).

Results

Preliminary experiments with interferon and yellow fever virus gave zones of inhibition of 20–30 mm. diameter in different experiments. With this virus, the boundary between the zone of plaque inhibition and the region of normal plaques was not very sharp; so the diameter of the zone could not be recorded very accurately. Similar results were obtained with influenza virus. Three other viruses were next examined in an experiment in which cultures were seeded with four different dilutions of each virus, with controls without interferon. Larger zones were seen with the two more slowly growing viruses, West Nile and Bunyamwera, as compared with the rapidly growing Western equine encephalomyelitis virus. Particularly sharp and clear zones were obtained with Bunyamwera virus. As can be seen from the table, the diameter of the zone of inhibition was inversely related to the dose of virus. A photograph of a plate which was infected with approximately 60,000 plaque-forming units is reproduced in fig. 1.

To determine the extent to which interferon could be diluted before the effect could no longer be demonstrated, duplicate

EFFECT OF VARYING THE VIRUS DOSE UPON THE SIZE OF THE ZONE OF INHIBITION. BUNYAMWERA VIRUS

Virus dose	Diameter of zone in mm.	Virus dose	Diameter of zone in mm.
60,000*	22	6000	23·5
19,000	22·5	1900	24

* Plaque-forming units per petri dish.

cultures were spotted with serial 5-fold dilutions of interferon. The diameters of the inhibition zones produced with Bunyamwera virus were measured on the fourth day after the application of the interferon beads. No effect was demonstrable with a 1/125 dilution. As is shown in fig. 3 the area of the zone of inhibition is directly proportional to the concentration of interferon.

When the interferon beads were applied eighteen to twenty-four hours after seeding with virus and incubating at 37°C, the zones of inhibition were reduced in size but were still measurable. When the plates were infected, treated with interferon, and incubated overnight at 25–30°C before being placed at 37°C, larger inhibition zones were produced. These experiments are being extended in a study with Dr. D. C. Burke and Dr. A. C. Allison designed to determine the size of interferon by its rate of diffusion.

It has been reported that interferon produced in cultures of calf kidney tissues is more active against influenza virus than interferon produced in cultures of chick-embryo cells when the test is carried out in calf cells, but that the position is reversed when the tests are carried out in chick tissues (Tyrrell 1959). In experiments reported in an accompanying paper, Dr. Isaacs and Miss Westwood (1959a) found that interferon prepared in rabbit tissue culture was effective against vaccinia virus when tested in the rabbit skin, whereas interferon prepared from chick-tissue culture had only a weak effect upon the same virus in the rabbit, although it was effective against vaccinia virus when tested on the chorioallantoic membrane of developing hens' eggs. The same two preparations of interferon were tested in parallel against vaccinia virus grown in chick cells in tissue culture using the plaque inhibition technique. No effect was demonstrable with the material prepared in rabbits, but clear inhibition zones 18 to 25 mm. in diameter were seen with the material prepared in chick tissues.

Discussion

The main advantage of this technique is its simplicity. It has been used to show the protective effect of interferon upon chick cells exposed to infection with six widely differing viruses. In the case of three of these, influenza, vaccinia and West Nile viruses, interferon activity had previously been demonstrated by other techniques (Isaacs and Lindenmann 1957, Isaacs and Westwood 1959a and b) and the extension of the range of activity is to be expected as further viruses are examined. Bunyamwera virus appears to be a suitable test organism for assaying interferon, though further studies may reveal more sensitive organisms. Greater precision may be obtained by the use of large trays allowing 36 or 64 samples to be examined under identical conditions.

Summary

The effect of an antiviral substance, interferon, was demonstrated by the development of a zone of inhibition of virus multiplication in a sheet of cells infected with a plaque-producing virus.

The area of the zone of inhibition is directly proportional to the concentration of interferon applied. Hence the technique may be used as a means of assay.

Thanks are expressed to Dr. A. Isaacs for the supplies of interferon, and to Dr. A. C. Allison and Mr. J. W. Lightbown for helpful suggestions.

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Preliminary Communications

URINARY LACTIC DEHYDROGENASE IN RENAL DISEASE

SINCE the lactic-dehydrogenase (L.D.) activity of kidney tissue is known to be high in relation to that of other organs, exceeding that of liver and heart,[1] one would expect renal cellular damage to release this enzyme into the blood and urine. In fact serum lactic-dehydrogenase (S.L.D.) activity is raised in various renal diseases,[2–4] in some of which cellular damage is prominent. No studies on the urinary L.D. activity U.L.D. in renal disease have hitherto been reported, apart from a reference by West and Zimmerman [4] to unpublished work in which they were unable to demonstrate such activity in the urine of patients with normal or high serum levels. This contrasts with our experience, and a summary of our results may therefore be of interest.

METHODS

All urinary enzyme determinations were performed upon 24-hour specimens of urine collected from normal subjects, including healthy hospital patients undergoing minor treatment, or from patients with renal disease. The urine specimens were centrifuged, and they were discarded if the deposit showed more than slight bacterial contamination. L.D. activity was determined usually within 4, and always within 12, hours of the 24-hour specimen being completed.

S.L.D. activities were determined by the spectrophotometric method of Wróblewski and LaDue,[5] and this was applied to the urine studies also, centrifuged urine (0·2 ml.) being substituted for serum (0·1 ml.). All centrifuged urine contained less than 0·5 mg. hæmoglobin per 100 ml.

Glutamic-oxaloacetic transaminase (G.O.T.) activity was determined in serum and urine by the method of Karmen et al.[6]

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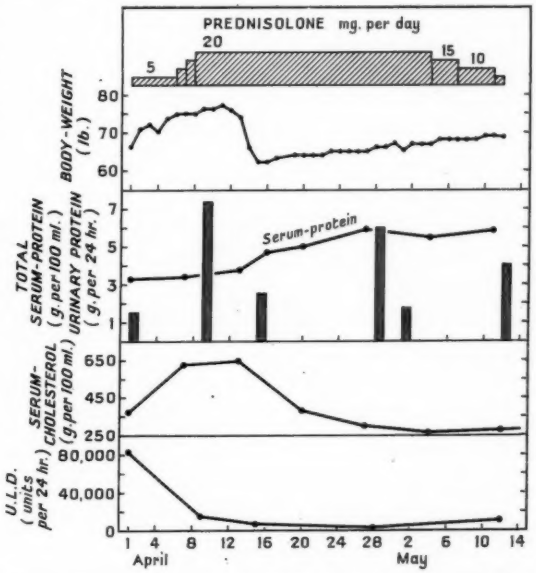

A comparison of urinary lactic dehydrogenase activity with other findings in a case of subacute glomerulonephritis treated with prednisolone.

ENZYMES IN URINE AND SERUM IN TWELVE CASES OF RENAL DISEASE

Case no.	Age	Sex	Diagnosis	U.L.D. (units per 24 hr.)	Urinary G.O.T. (units per 24 hr.)	S.L.D. (units per ml.)	Serum G.O.T. (units per ml.)
1	18	M	Diuretic phase of acute tubular necrosis	140,000	..	550	23
2	8	M	Exacerbation of subacute glomerulonephritis	82,000	15,000	290	17
3	8	F	Acute glomerulonephritis	130,000	..	500	21
4	60	F	Subacute glomerulonephritis	37,000	13,000	250	21
5	57	M	Amyloid nephrosis, terminal phase	48,000	8000	470	20
6	62	M	Diuretic phase of acute tubular necrosis	33,000	..	1600	20
7	29	M	Acute glomerulonephritis, recovery phase	37,000	9000	300	18
8	71	F	Myelomatous nephropathy	30,000	..	400	17
9	15	M	Nephrotic syndrome	92,000	17,000	300	29
10	45	M	Nephrotic syndrome, quiescent phase	7000	..	220	12
11	68	M	Chronic glomerulonephritis	7000	..	240	14
12	56	M	Chronic pyelonephritis	12,000	..	280	10
Normal range				7000–32,000	<5000	150–500	5–35

Temperature corrections for L.D. and G.O.T. activity were applied throughout; the values quoted represent activities corrected to a temperature of 25°C.

In this laboratory the normal value for serum L.D. activity is 150–500 units per ml., and for G.O.T. activity 5–35 units per ml.

RESULTS

Normal Subjects

The mean U.L.D. activity of fifteen healthy adults was found to be 16,000 units per 24 hr., with a standard deviation of ±7500 units per 24 hr. (range 7000–32,000 units per 24 hr.). The excretion of U.L.D. appeared to be fairly constant throughout the collection period, for determinations made on random samples forming part of the 24-hour specimens showed the enzyme concentrations to be within 10% of the total 24-hour value.

Kidney tissue possesses G.O.T. activity,[7] and this was detected also in normal urine, but in much smaller amounts than U.L.D. activity. The amounts observed were so small that the errors inherent in the method were disproportionately large. No mean figure can be given, but the highest value was less than 5000 units per 24 hr.

The presence of G.O.T. and L.D. in the urine of normal people is probably the result of normal "wear and tear" breakdown of cells in the urinary tract. Animal experiments [4 8] indicate that serum L.D. and G.O.T. are not normally excreted by the kidney, and we observed no increase of urinary L.D. or G.O.T. activity in three cases of myocardial infarction in which there were high serum levels of these enzymes.

Patients with Renal Disease

Twelve patients with renal disease were investigated (see table). Cases 1–9 had acute renal disorders which might be associated with kidney-cell necrosis, and eight of these were found to have U.L.D. levels above the normal range. Serial U.L.D. determinations were performed on three of these patients, and enzyme activities were found to return to normal roughly in parallel with, or just before clinical and other laboratory evidence of improvement of the kidney condition. The figure illustrates this in a case of subacute glomerulonephritis treated with prednisolone.

Cases 10–12, all with static longstanding renal disease, had normal U.L.D. levels.

The urinary deposits of both freshly voided and the 24-hour urine specimens were examined in the cases with increased U.L.D. activity. Cells and casts were absent or scanty except in cases 3 and 7, whose deposits contained large numbers of red and white cells. It was shown, by adding similar quantities of intact red and white cells to normal urine, that these would not raise the U.L.D. activity. Determination of the hæmoglobin content of the centrifuged urine excluded red-cell hæmolysis as the cause, for the addition of hæmolysates to normal urine did not increase the U.L.D. activity if the hæmoglobin level remained below 0·5 mg. per 100 ml. urine.

There was no correlation between the U.L.D. activity and the degree of proteinuria, for independent variation was found both in the same individual and from one patient to another.

The urinary G.O.T. activity also was raised in those cases of renal disorder in which this determination was performed (see table). A comparison of the average urinary ratio of L.D./G.O.T. (5/1) with that of serum (16/1) suggests that these enzymes are unlikely to have reached the urine by leakage through damaged glomeruli. If this were so similar ratios might be expected in both serum and urine.

CONCLUSIONS

We conclude therefore that these L.D. and G.O.T. enter the urine as a result of renal cellular breakdown, and that the U.L.D. activity may be a measure of its extent; a raised U.L.D. activity appears to indicate active renal cellular injury.

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EFFECT OF PARATHYROID EXTRACT ON RENAL CONCENTRATING ABILITY

Epstein and his colleagues [1] have recently shown that in dogs the renal concentrating ability can be much reduced by injection of parathyroid extract. This effect, which was accompanied by a rise in the serum-calcium level, was characterised by a decrease in the maximal urine/plasma (U/P) osmolal ratio obtained after food and water restriction and administration of pitressin. A diminution in the maximal tubular capacity for water reabsorption $\left(T^{C}_{H_2O}\right)$ during osmotic diuresis was observed also.

The publication of this work prompts us to report our almost identical observations on renal concentrating-power in one healthy human subject given parathyroid extract by intramuscular injection. During these observations she had a constant diet, and measurements of maximal U/P osmolal ratio were made after 20 hours of water and food deprivation. At the beginning of this period of dehydration, pitressin tannate 20 units in oil was given. Measurements of $T^{C}_{H_2O}$ were made under similar conditions of water deprivation, during the course of which an osmotic diuresis of 4–15 ml. per minute was induced by the intravenous infusion of 15% mannitol.

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EFFECT OF PARATHYROID EXTRACT
(The subject was a woman of 43 weighing 51 kg.)

Experimental conditions	U/P osmolal ratio	$T^C_{H_2O}$ (ml. per min.). Average of 7–9 clearance periods	Serum-calcium (mg. per 100 ml.)	24-hour urinary calcium excretion (mg.)	Creatinine-clearance (ml. per min.)
Control	3·9 4·0	6·7	9·1	218	99
'Parathormone'* 1000 units I.M. per day for $3^1/_2$ days	3·0 2·4	5·3	12·5	..	92
Parathormone 1000 units I.M. per day for $6^1/_2$ days	1·5 1·4	2·9	11·7	498	98
5 days after stopping parathormone	2·2	4·5	10·0	235	120

* Parathyroid extract (Lilly) U.S.P. units.

The table gives the values for the maximal U/P ratio and for $T^C_{H_2O}$ in ml. per min. after parathyroid extract had been given for $3^1/_2$ and $6^1/_2$ days, and it includes the values for serum-calcium, urinary calcium, and creatinine-clearance. The results show a significant depression in the ability of the kidneys to conserve water, both at endogenous solute loads and during osmotic diuresis. This effect was partially reversed 5 days after the parathyroid extract was stopped. There was no significant depression in creatinine clearance, and there was no change in the blood-urea-nitrogen level, which remained within normal limits throughout the study.

Taken in conjunction with those of Epstein et al.[1] on dogs, these observations suggest that this functional limitation of water conservation may be partly responsible for the polyuria commonly found in patients with hyperparathyroidism. This view is consistent with the few clinical observations that have been made on the improvement in renal concentrating power shortly after removal of a parathyroid tumour.

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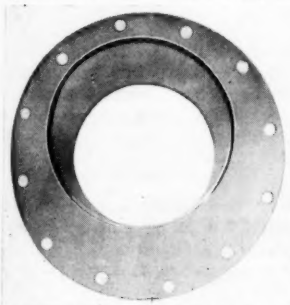
New Inventions

A LABOUR-SAVING PLATE FOR THE MELROSE HEART-AND-LUNG MACHINE OXYGENATOR

THE oxygenator devised by Melrose[1] has been used in the U.S.A.[2] and this country.[3] This artificial lung consists of circular plates of 'Perspex' bolted together to form a cylinder. Perspex washers separate individual plates, allowing them to project into the lumen of the cylinder as blades which increase the surface on which blood forms a film.



The time required for cleaning and assembling the oxygenator has been greatly reduced in this centre by routine use of the perspex artificial lung segments here illustrated. Each segment has the form of an oxygenator plate and its own washer. The surface area available for oxygenation is not reduced in an oxygenator made from these segments. The lung has proved satisfactory in patients whose surface area ranged from 1·02 to 1·82 sq. m.; and there has been no evidence of excessive hæmolysis, fibrinogen loss, foaming, or damage to the clotting mechanisms of the blood.

These segments are made by Lusterlite Products Ltd., 56, Devon Road, Leeds 2.

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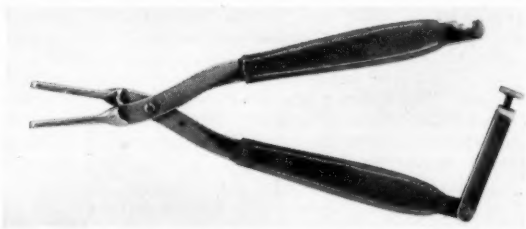
A HAND CLAMP FOR PLASTIC TUBING

IN using an extracorporeal circulation it is desirable to close soft or stiff plastic tubing with a clamp which will not damage the tubing and which may be locked against unwitting removal. The clamp illustrated has proved satisfactory in use with tubing measuring from $^1/_4$ to 1 in. in bore. The jaws are milled and measure 3·3 × 1 cm. The handles are 15 cm. in length. A steel stirrup hinged on one handle may be slipped over the other in the closed position, and locked in place by means of a milled screw.



The clamp is made by Chas. F. Thackray, The Old Medical School, 10, Park Street, Leeds 1.

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2. Gerbode, F., Osborn, J. J., Melrose, D. G., Perkins, H. A., Norman, A., Baer, D. M. *Lancet*, 1958, ii, 284.
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Reviews of Books

Human Nutrition and Dietetics

Sir STANLEY DAVIDSON, B.A. Cantab, M.D. Edin., F.R.C.P., F.R.C.P.E., former professor of medicine and clinical medicine, University of Edinburgh, and physician-in-charge, Royal Infirmary, Edinburgh; A. P. MEIKLEJOHN, M.A., D.M., B.SC. Oxon., M.R.C.P., lecturer in nutrition in the university; R. PASSMORE, M.A., D.M. Oxon., reader in physiology in the University. Edinburgh: E. & S. Livingstone. 1959. Pp. 844. 84*s*.

THIS new book on human nutrition, fundamental and applied, has been written to help those who wish to apply current scientific knowledge about food and metabolism to the well-being of man whether in health or disease. It begins therefore with fundamentals—the composition of the body and of food, the physiology of appetite and satiety, nutritional requirements so far as they are really known, and nutritional dangers, some of them too well known. The authors then pass on to the great physiological disorders which have made nutritional history—obesity, kwashiorkor, rickets, and beriberi. A long section follows on the dietary treatment of the humdrum illnesses we know so well in daily practice, such as fever, allergy, nephritis, diabetes, and gout. It contains specimen diets and other practical advice. The next section deals with nutritional aspects of public health, its triumphs in preventive medicine, its future tasks among the rising populations of the world, and its famine warnings from the past.

The book ends with a section on the nutritional problems of pregnancy, lactation, of great performances in athletics, and of climatic extremes. The references are given as footnotes on each page and there is a good index.

In writing this readable, interesting, and knowledgeable book, the authors have achieved an admirable unity of purpose and presentation. Without being in any sense parochial, moreover, the book has a pleasant local and personal flavour unlike the soulless compendiums of international literature which confront us all too often today.

The Clonal Selection Theory of Acquired Immunity

Abraham Flexner Lectures of Vanderbilt University, 1958. Sir MACFARLANE BURNET, O.M., F.R.C.P., F.R.S., director, Walter and Eliza Hall Institute of Medical Research, Melbourne. Nashville, Tennessee: Vanderbilt University Press. London: Cambridge University Press. 1959. Pp. 209. 22*s.* 6*d.*

IN these lectures Sir Macfarlane Burnet describes a general theory of immunity developing from the ideas of Ehrlich, Jerne, and Talmage. According to the clonal selection theory, there exist in the animal groups of mesenchymal cells which carry immunologically reactive sites corresponding to various potential antigenic determinants. When they come into contact with the corresponding antigen, the appropriate cells are stimulated to divide and form a clone of cells capable of producing antibody to the particular antigen. In other words cells capable of producing antibody to the large number of potential antigens exist within the body before contact with the antigen. This is the essence of a selection theory in contrast to generally accepted theories of immunity, according to which antibody is synthesised *de novo* after contact with the appropriate antigen.

In the light of this selection theory Burnet examines many normal and pathological immune responses and shows that they fit the hypothesis of clonal selection as well as (and sometimes better than) earlier hypotheses of antibody formation. To some extent the argument must end there until critical experiments can be designed to distinguish hypotheses of the two kinds. But it points to an area of ignorance about basic immunological phenomena and to the need for research which may have important applications to medicine. Those who are concerned with pathological immune responses, as seen in Hashimoto's disease, acquired hæmolytic diseases, and the collagen diseases, should find some useful ideas in this book.

Inborn Errors of Metabolism

DAVID YI-YUNG HSIA, M.D., associate professor of pædiatrics, Northwestern University Medical School; director, genetic clinic, Children's Memorial Hospital, Chicago. Chicago: Year Book Publishers. London: Interscience Publishers. 1959. Pp. 358. 72*s.*

THIS book proudly takes the title of A. E. Garrod's classic, but it hardly does him justice by stating " that half a century later rapid progress in the basic sciences has given body and substance to what was, by necessity, supposition in Garrod's time ". No-one can doubt the tremendous progress made, but the historian of 20th-century science will ascribe to Garrod's work rather more " body and substance " than Dr. Hsia's remark might imply.

The book will be particularly useful to the non-expert who wants to inform himself quickly and reliably about the inherited disturbances of metabolism, and to the medical student for its brief and clear explanation of basic genetic concepts, followed by a catalogue of the known disorders—disturbances in molecular structure, in which the hæmoglobinopathies are prominent; disturbances in molecular synthesis, which include deficiency of cœruloplasmin (Wilson's disease) and a wide variety of clotting-factor deficiencies; and disturbances in molecular function (enzyme defects). This part is the most extensive and includes enzyme defects in aminoacid and carbohydrate metabolism, and in the metabolism of hormones and pigments. Maple-sugar-urine disease, which has recently been described, is included in the disturbances of aminoacid metabolism. The detailed investigations of oxaluria coming from the department which produced the original *Inborn Errors of Metabolism*, which trace it to an abnormality of glycine metabolism, have not yet found a place. The section on disturbances in carbohydrate metabolism includes a welcome account of glycogen storage disease, and some readers might be surprised to learn that hereditary spherocytosis is now considered to be essentially an abnormality of the carbohydrate metabolism of the red cell. The congenital methæmoglobinæmia type II, which is due to an abnormal globin, should have been listed with the hæmoglobinopathies rather than with the disturbances in pigment metabolism.

There is one chapter on the disturbances in renal transport in which renal glycosuria and multiple defects (such as Fanconi's syndrome) are included. Some 50 pages are given to conditions in which the ætiology is unknown, and they are primarily the congenital abnormalities of lipid metabolism. There is also an excellent and concise account of the muscular dystrophies, although here one might justifiably ask why there should be an error in *metabolism*. A stimulating review of the future of biochemical genetics includes a list of disorders which may turn out to be genetically determined. There is also an appendix giving laboratory methods which might be useful in the detection of inborn errors of metabolism.

International Textbook of Allergy

Editor: J. M. JAMAR, M.D., lecturer, University of London. Oxford: Blackwell Scientific Publications. 1959. Pp. 639. 110*s.*

THIS work, to which thirty-one writers have contributed, is both comprehensive and authoritative; but almost inevitably the chapters differ in style and merit. The first part deals with the mechanisms of allergic reactions; and the second part with clinical topics such as hay fever, asthma, allergic diseases of the skin, gastrointestinal tract, and eye, and the role of allergy in blood diseases, drug reactions, and vascular and collagen diseases. Other chapters describe treatment with specific hyposensitisation, anti-histamines, and corticotrophin and adrenocortical steroids. Despite its drawbacks this book provides a useful source of information, and most readers will find in it something to interest them.

Memoirs of the Society for Endocrinology (*No. 6: Implantation of Ova.* London: Cambridge University Press. 1959. Pp. 97. 30*s.*).—This memoir, edited by Dr. P. Eckstein, records the proceedings of a symposium held in London in November, 1957. Very well produced, it surveys a vital phase of mammalian development during which the fertilised ovum lies free in the uterine cavity and subsequently becomes embedded in the endometrium. The eighteen contributors were drawn from several disciplines, thus enabling them to consider morphogenetic, histochemical, physiological, biochemical, hormonal, and pharmacological aspects in the light of recent research, much of it previously unpublished. An opportunity is thus provided for assessing and comparing these varied analyses of the same topic as the results of different methods and approaches are unfolded. One is struck by the evolving pattern of chemical change, running parallel to the changes that can be observed in terms of morphogenesis. Moreover, the histological and morphogenetic reactions and interactions concerned in implantation appear to be specific, whereas the physiological processes involved seem to be more generalised. Another feature emerging from these contributions is the relative autonomy within the uterus of the unimplanted fertilised ovum, and this represents a significant contribution to knowledge. The report contains much information regarding the mechanical, chemical, and hormonal factors concerned with or affecting implantation. The pharmacological procedures interfering with implantation and subsequent development stimulate much speculation about their possible use in the investigation not only of the mechanism of implantation, but also of placental function, teratogenesis, and the control of growth.

THE LANCET

LONDON 12 SEPTEMBER 1959

Sickle Cells

THE basis of sickle-cell disease is the presence of an abnormal hæmoglobin molecule which in its reduced state forms aggregates. A multimolecular combination of this hæmoglobin, being much less soluble than single molecules, becomes a solid gel; this is birefringent and its constituents form a large tactoid. When such tactoids are assembled inside the erythrocyte their rigidity is reflected in distortion of the cell, which then becomes a sickle-cell. Because of its abnormal shape the sickled cell is susceptible to mechanical destruction and to attack by phagocytes, resulting in hæmolytic anæmia. In addition the spiked cells can cause tissue damage by blocking blood-vessels; occlusion of small vessels causes the crises of sickle-cell disease. When only genes for sickle-cell hæmoglobin are present the hæmoglobinopathy is severe—sickle-cell anæmia. In the sickle-cell trait with genes for hæmoglobins A and S the hæmoglobin mixture contains more A than S. In vivo there is no aggregation of deoxygenated hæmoglobin molecules, and no anæmia results. With one gene for hæmoglobin C and one for S (hæmoglobin-C disease) the average proportion of S is higher than in the sickle-cell trait; molecular aggregation occurs more easily and the life-span of the erythrocytes is reduced, though the hæmolysis is less severe than in sickle-cell anæmia.

ITANO [1 2] has shown that the degree of sickling does not depend entirely on the proportion of hæmoglobin S in a red cell. The insoluble aggregates formed from A-S mixtures are larger than would be expected from solubility measurements of pure A and pure S solutions. Thus 50 mg. of reduced hæmoglobin A dissolves completely in 10 ml. of 2·24*M* phosphate buffer; but if a mixture of 30 mg. of A and 20 mg. of S is equilibrated in the same volume of buffer the total hæmoglobin in solution is only 14 mg. This indicates that a stabilising action in the solid phase prevents more than half the available hæmoglobin A from going into solution. Although reduced hæmoglobin C is more soluble than reduced hæmoglobin A, an S-C mixture with 40% hæmoglobin S is less soluble than the corresponding A-S mixture. The greater stability of S-C aggregates may explain the considerable difference in sickling tendency between sickle-cell trait and sickle-cell hæmoglobin-C disease. Though the latter is a definite hæmoglobinopathy the anæmia and the incidence of crises are less than in the homozygous sickling condition. The disorder often remains undiagnosed because the hæmolysis is countered by increased activity of the bone-marrow; but an additional demand on reserves—for instance, in bronchopneumonia or pregnancy—may disclose the handicap. We publish this week an article by Dr. DIAMOND in which she describes the unexpected flare-up of sickle-cell hæmoglobin-C disease in West Indian patients. In West Indian or African immigrants sickle-cell hæmoglobin-C disease or sickle-cell thalassæmia should be suspected whenever they show an atypical response to infections or pregnancy.

Reports on sickle-cell disease in pregnancy have been contradictory. In 1949 ANDERSON and BUSBY,[3] reviewing their experience at the Johns Hopkins Hospital, Baltimore, concluded that the outlook for women with sickle-cell anæmia was more favourable than had hitherto been supposed. CURTIS, of the Johns Hopkins Hospital,[4] and ABRAMS et al.,[5] of the Jefferson Medical College Hospital in Philadelphia, differ from SACKNER et al.,[6] of the Philadelphia General Hospital, in considering that sickle-cell hæmoglobin-C disease gives rise to more complications than the clinically more severe sickle-cell anæmia. This is not easily understood. Possibly the patients with sickle-cell anæmia had been known for some time to have a hæmoglobinopathy and had been closely observed, whereas in the women with sickle-cell hæmoglobin-C disease the hæmoglobinopathy was a more sudden and unexpected complication. Women with untreated hæmolytic anæmia in whom the red-cell loss was offset might have been using up larger reserves of hæmopoietics; and they would then have been especially liable to suffer from a subclinical folic-acid deficiency, which often remains unrecognised. Professor DACIE and his colleagues [7] have pointed out that megaloblastic change due to folic-acid deficiency occurs in hæmolytic anæmias, and though not common may be more frequent than has been assumed. Alternatively in at least some of the cases sickle-cell thalassæmia may have been mistaken for sickle-cell anæmia. The diagnosis of the homozygous state was not based on family studies but was made entirely from the electrophoretic pattern of the hæmoglobin. Sickle-cell anæmia cannot be definitely distinguished from sickle-cell thalassæmia by paper-electrophoresis, because these two disorders can produce identical patterns. A family study is necessary in order to establish beyond doubt that one or the other is present.[8] It is perhaps not easy to understand why, despite identity of electrophoretic patterns, the two clinical states should be so different. ITANO's work may explain the paradox; for amounts of hæmoglobin A too small to be recognised by paper electrophoresis may yet enhance the tendency of sickle-cell-hæmoglobin molecules to aggregate.

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Adjustments to Postural Change

AN upright position necessitates special adjustment of the circulatory system if consciousness is not to be lost. Fortunately failure of the adjustment mechanism is uncommon. When normal people assume a head-over-feet position the venous return to the heart is reduced owing to the pull of gravity on the blood below the heart; this reduces the cardiac output; the pulse-rate then reflexly increases; and the diastolic pressure rises, indicating that peripheral vasoconstriction has taken place. Some of these responses to postural change were noted towards the end of the 19th century.[1 2] In the '20s and '30s of this century it became clear that the calibre of both arteries and veins was reflexly regulated through the medullary vasomotor centre, which received information from sensory nerves whose ends lay in the aortic arch and carotid sinuses.[3] Possibly these pressoreceptor areas are the most important in the body since they are close to the heart and guard the supply to the central nervous system. But other vascular areas, too, are sensitive to pressure or tension changes—for instance, the mesenteric region,[4] since compensatory blood-pressure responses can be induced in anæsthetised animals whose sinus nerves and vagi have been cut.[5]

The conditions in the lower limb when first the erect position is assumed have been summarised by SUNDIN.[6] The arteries of the foot must contend with the usual 100 mm. Hg pressure plus 70–80 mm. Hg due to gravity, and the capillaries are faced with about 110 mm. Hg opposed only by 3–4 mm. Hg tissue pressure. Unless these forces are rapidly counteracted there must be a mass loss of plasma by diffusion. On prolonged standing syncope is well known to occur even in healthy young adults; so the initial compensation is not always maintained. The reason for the delayed failure is still unexplained. For experimental purposes syncope due to postural hypotension can be induced by passive tilting; and it has been shown that if blood pooling is prevented by bandaging the legs and thighs before tilting, then syncope is prevented.[7] Nevertheless, it is not the volume of blood pooled which leads to hypotension, but some abnormality of the adjustment mechanism.[8] This was demonstrated by rapidly inflating tourniquets round the thighs of an erect patient whose blood-pressure had fallen to below 50 mm. Hg. On returning the patient to the horizontal, with the blood still trapped beyond the tourniquets, the blood-pressure rose to a normal level.[8] From records of forearm blood-flow it can be seen that in normal subjects tilting causes a rapid reflex vaso-constriction, which in many people is sufficient to maintain the mean blood-pressure.[7] Likewise, blood-flow in the toe decreases when the leg is below heart level, and is also less when the foot is level with the heart than when it is raised above it.[9] These findings are contrary to mechanical expectations, but reasonable on physiological grounds. By contrast, when subjects with postural hypotension are tilted the blood-pressure falls rapidly, the heart-rate does not quicken, and there is little or no constriction of the blood-vessels of the hand, even in cases where various tests suggest that the peripheral vasomotor nerve-supply is normal.[8] Nevertheless, the sympathetic nervous system is obviously important in compensatory vasoconstriction, since the limb blood-vessels do not constrict on tilting patients who have undergone cervical sympathectomy [7] or in normal subjects with deep block of the forearm nerves.[10]

With the knowledge that the effects of sympathetic nerve stimulation are, with few exceptions, mediated by the liberation of noradrenaline as the chemotransmitter,[11] a new tool became available for the study of circulatory responses. Methods were developed for assay of adrenaline and noradrenaline in blood [12] and the overspill of these hormones in the urine.[6] The latter method, though indirect, has advantages, and both methods lead to the same conclusion—that when normal people are tilted the concentration of adrenaline is increased in both plasma and urine, and that the quantities found correlate directly with the angle of tilt.[6 12] The increase in production of adrenaline by the adrenal medulla is due to stimulation of the sympathetic nerve-supply to the gland, and the increase in noradrenaline is due to increased general activity of the sympathetic vasomotor nerves.[6 12] Relative to this, an interesting difference was noticed between a subject who had been adrenalectomised and one who was sympathectomised. On tilting, the former had an immediate fall in blood-pressure soon followed by a rise, no increase in the adrenaline concentration of the blood, but an increase in the noradrenaline; whereas the sympathectomised subject reacted like patients with postural hypotension, and showed a progressive fall in blood-pressure and no significant change in either the adrenaline or noradrenaline of the plasma.[12] In normal people, then, in the erect position systolic pressure is maintained by an increase in sympathetic activity which, by causing vasoconstriction in muscle vessels, raises diastolic pressure and increases the pulse-rate. If the erect position is passively maintained some normal people sooner or later faint, with prodromal signs of sweating, pallor, and sighing respiration, and, immediately before the faint, sudden bradycardia. The faint may occur even in the presence of a high blood level of noradrenaline.[12] This is the still unexplained syndrome which LEWIS [13] termed vasovagal, and which is not seen in subjects with postural hypotension. These people faint rapidly with no sign of excessive autonomic activity.

Electroencephalographic records taken during tilting experiments showed that in normal subjects there was

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a brief disappearance, then reappearance, of alpha activity.[12] In patients, the tilting brought out localised slowing in areas where the case history suggested there was probably some focus of cerebrovascular disease. In the absence of evident cerebrovascular disease postural hypotension gave rise to diffuse slowing.

It now seems clear that there are sensory endings in the thorax, in the low-pressure part of the cardiovascular system, which respond to a shift in blood-volume. These endings are sometimes referred to as volume receptors, but probably, in fact, are sensitive to changes in pressure or in distension of the vessel walls.[3] Possibly these receptors initiate the severe peripheral vasoconstriction sometimes seen in congestive heart-failure.[14] This is an example of a normally useful reflex response whose persistence in abnormal conditions is undesirable. The same endings are almost certainly part of the mechanism concerned in counteracting the high G force developed when human beings are rapidly centrifuged. Individuals differ in their ability to withstand high rates of acceleration, and those who can produce a high plasma-noradrenaline concentration seem to be the most resistant.[12] There is also other evidence that a shift of blood-volume fires off reflex responses from these, or other, thoracic receptors[3]—for example, a change in the rate of urine flow. Severe bleeding, too, gives rise to a state of affairs similar to postural hypotension, and leads to many of the same physiological responses. Nor must it be forgotten that mechanical factors which hinder the venous return to the heart can also cause hypotensive attacks—as, for instance, in late pregnancy, and occasionally in normal subjects when they stand in a lordotic position.[7]

What is not always clear is just where the lesions lie which give rise to disorders of the postural adjustment mechanism. Sometimes other disturbances are present at the same time, such as in sweating and response to body-temperature changes, and in bladder function—suggesting a fairly general pathological change. That the plasma-catechol-amines do not rise on tilting in cases of postural hypotension does not prove that the lesion is one of the peripheral vasomotor system: in fact, STEAD and EBERT[8] found evidence to the contrary. Sometimes lesions in the spinal cord, as in syphilis, may be responsible.[7] There is little information regarding disorders of the thoracic receptor mechanisms. On the whole, it seems probable that the disease process is a central one—perhaps a selective disturbance of hypothalamic sympathetic areas, since reflexes using the same final common path are not affected.[8]

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Annotations

THE WOLFSON GRANT

NEVER in its 441 years has the Royal College of Physicians of London had so splendid a gift as the one now made by the Isaac Wolfson Foundation. With £450,000 coming to it over the next seven years, the college can have a really good building, really suited to its needs. These needs are very different from what they were when its present house in Pall Mall East was built in 1825. With a tenfold increase of fellows, and the addition of some 4000 members, the college has latterly found new life and purpose, of which its series of influential reports, its creation of the Association for the Study of Medical Education (ASME), and its recent college conferences are notable manifestations. Development, however, has often been checked by lack of the space and staff it would require. The great merit of the Wolfson grant is not only that the college can have a finer building; for a building could be static. It is that, with the other funds thus freed or collectable, the college will now have money enough to make dynamic use of its new home and its new opportunities. The same kind of enterprise and vision that have gone into the creation of a great postgraduate centre by the Royal College of Surgeons can be applied by the Physicians no less usefully though in a different way. But the necessary metamorphosis depends on the college bursting out of its constrictive exoskeleton beside Trafalgar Square and forming something more flexible in Regent's Park. The process is to begin when the site of Someries House can be taken over in 1961.[1]

In medicine we already had much cause to be grateful to the Isaac Wolfson Foundation. Since it was founded in 1955, its grants have included £250,000 to the Westminster Hospital for the school of nursing, £150,000 to the British Empire Cancer Campaign, £125,000 to the Postgraduate Medical School of London, and £184,000 to the Institute of Psychiatry at the Maudsley Hospital. The benefits of the present benefaction are less direct but in the long run could prove greater. Most of us in this country feel that a national medical service, publicly provided, must in the end become mediocre unless it is inspired by professional ideals and balanced by strong professional organisations. Mr. Wolfson and his fellow trustees have strengthened the oldest of these professional bodies.

1. *Lancet*, 1959, i, 721.

HYPOVENTILATION

RESPIRATORY minute volume may be diminished at the peripheral or at the central level. Peripheral causes of hypoventilation include weakness or paralysis of the respiratory muscles, fixity or deformity of the thoracic cage, and inefficient perfusion of the pulmonary aveoli, while centrally the respiratory centres are often depressed by mechanical trauma. Chronic hypoventilation with reduction of the oxygen content of arterial blood induces secondary polycythæmia. A further result is retention of carbon dioxide, often manifest in lassitude and headache. It should be noted that, though carbon-dioxide retention is always detectable in arterial blood, hypercapnia caused by perfusion defects will not be reflected in the expired air.[1]

Recently cases have been described which present with cyanosis, polycythæmia, right-heart failure, and headache, lassitude, and muscular twitching. The clinical picture is similar to that of the cardiopulmonary syndrome of gross obesity (" Pickwickian " syndrome)[2] but these patients are not fat. Whereas in hypoventilation with gross obesity the disturbance of pulmonary function is thought to be due to the masses of adipose tissue embarrassing respiration mechanically, the cause of this new syndrome

1. Robin, E. D., Julian, D. G., Travis, D. M., Crump, C. H. *New Engl. J. Med.* 1959, **260**, 586.
2. Burwell, C. S., Robin, E. D., Whaley, R. D., Bickelmann, A. G. *Amer. J. Med.* 1956, **21**, 811.

is held to be in the respiratory centre.[3] Rodman and Close,[4] reporting a further case, adduced more evidence of the unresponsiveness of the respiratory centre. In most hypoventilatory conditions, the breathing of oxygen-enriched air is followed by a prompt though transient decrease in pulmonary ventilation. This is attributed to the cessation of "hypoxic" impulses from the carotid-body chemoreceptors. Failure of the hypoventilatory response to "physiological denervation"[5] of the carotid chemoreceptors indicates a lesion of the chemoreceptors, of the medullary centres, or of their neural connections.

Patients presenting with polycythæmia and disordered pulmonary ventilation without obvious heart or lung disease need careful investigation. Primary polycythæmia can be excluded by studies of arterial oxygen saturation, which is normal in polycythæmia vera. If the polycythæmia is secondary, the response to breathing 100% oxygen may give valuable information: lack of an initial hypoventilatory response indicates unresponsiveness of the medullary centres, while failure to relieve cyanosis may indicate an occult right-to-left shunt.[6] Similarly arterial carbon-dioxide estimations are valuable. Primary hypoventilation syndromes are marked by retention of carbon dioxide, but this hypercapnia is not found with right-to-left shunts or diffusion defects. Now that pulmonary function is more often estimated, disturbances of pulmonary ventilation are more likely to come to light.

OUTLOOK FOR DENTISTRY

THE Central Youth Employment Executive has added a booklet on dentistry to its Choice of Careers series.[7] Discussing the opportunities open to the qualified dentist, the booklet says:

"There is at present a shortage of dentists, which it is expected will increase, because the number of students in training is not sufficient to replace the large number of dentists who will be retiring from practice during the next few years. Newly qualified dentists, women as well as men, have therefore a wide choice of opportunities."

We must all hope that this shortage will be an attraction to entrants; but it is certainly going to be an inconvenience, or worse, to the public. Pointing out that last year the number of names on the Dentists Register fell by 191, and that no less than 27% of dentists engaged in the General Dental Service were 60 years of age or over, the *British Dental Journal*[8] urges the Government to provide money for a national campaign of dental health education and to give priority for the extension of the dental schools, so as to increase the number of students in training. Since it is generally agreed that dental disease is increasing rapidly, the journal foresees a complete breakdown of the nation's dental services unless the Ministry of Health does more to instruct the public in positive dental health —perhaps by liberally supporting the work of the Standing Committee on Dental Health Education, which at present gets no financial help whatever from the Government. In addition, the expansion of the dental schools must be treated as a metter of urgency, since seven or eight years must elapse between the commencement of a building programme and the appearance on the Dentists Register of the name of the first additional dentist.

Plainly, the situation will deteriorate further before any improvement can be expected from policy decisions taken now, however radical these may be. The experimental scheme for training dental ancillaries, which might have brought some relief to the dental profession by relieving the dentist of some of his simpler and routine tasks, seems to make little progress; and, though the findings of the Royal Commission on the Remuneration of Doctors and Dentists, when eventually these are known, may make dentistry more attractive as a career, their effect on the number of practising dentists could not be felt for a long time.

Additional difficulties arise from the uneven geographical distribution of dentists. While some parts of the country have more than their fair share, the situation in other, less favoured areas already fully justifies the alarm expressed by the dental profession in discussions on public-health policy. To give one recently reported example, the Shetland Isles have had no dentist at all in the past year except the school dental officer.[9]

MENTAL HEALTH OF THE ELDERLY

THIS disturbed world is not an easy place in which to grow old, and in the post-war battle for priority the social services which should support the elderly have never caught up with their needs. Hence what might be merely an emergency often grows into a crisis or a catastrophe, and for lack of the right help many an old man (or woman) becomes a reluctant, and often inappropriate, occupant of a bed in one of our overcrowded mental hospitals. The strain which old people are imposing on the social and health services suggests that, though we have lengthened life a little, we have not yet learnt to put the few extra years to the best use. The expansion of the geriatric services, research into the physiological process of ageing, and various expert reports are signs of the community's growing concern. The latest of these reports,[10] from the World Health Organisation, nominally deals with the mental health of the aged; but, since mental and physical health are interdependent, and both are influenced by social circumstances, it inevitably surveys most of the difficulties of old people.

All over the world the old have to face the common difficulties of dwindling resources of money, health, resilience, and friends; but these difficulties are often less in the traditional cultures, now found chiefly in what are called the less-developed countries. The W.H.O. committee believe, however, that, as industrialisation thickens, the traditional pattern will have to change and that only careful advance planning will protect old people in these countries. Certainly in our part of the world urbanisation and industrialisation have often increased their troubles. Though there may be savings and pensions, their real value is apt to fall; younger members of the family have been drawn away from their old homes to new centres of employment, and daughters and other forms of domestic help are working all day in factory or office. The old person easily becomes bewildered by the pace and complexity of modern life, especially as exemplified by traffic and income-tax forms.

The W.H.O. committee, not unexpectedly, agree that the best prophylaxis against ageing (as distinct from old age) is independence and activity. One of the easiest ways of achieving this is to postpone retirement as long as

3. Richter, T., West, J. R., Fishman, A. P. *New Engl. J. Med.* 1957, **256**, 1165.
4. Rodman, T., Close, H. P. *Amer. J. Med.* 1959, **26**, 808.
5. Dripps, R. D., Comroe, J. H., Jr. *Amer. J. Physiol.* 1947, **149**, 277.
6. Friedlich, A. L., Bing, R. J., Blount, S. G. *Bull. Johns Hopk. Hosp.* 1950, **86**, 20.
7. Choice of Careers: new series. no. 96. Dentistry. H.M. Stationery Office. 1959. 9*d*.
8. *Brit. dent. J.* Aug. 4, 1959, p. 47.
9. *Scotsman*, Aug. 12, 1959.
10. Mental Health Problems of Aging and the Aged. *Wld Hlth Org. tech. Rep. Ser.* no. 171. Geneva; 1959. Pp. 51. 3*s*. 6*d*. (Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.)

possible, and here a contribution to the wellbeing of old people can be made by industry. As Mr. F. Le Gros Clark asks in the latest of his studies [11] on ageing in modern industry, "how far will a highly mechanised industry be able to absorb ageing men who can no longer carry out their normal work"? He believes that of manual workers who retire at sixty-five 10–15% lack the urge or the opportunity to find alternative lighter work and a further 10% retire by custom rather than inclination. The W.H.O. committee estimate that a third of retired people in Great Britain are fit and willing to work and could make a valuable contribution to the stability of industry.

In their review of mental disorders proper, the committee suggest that the prognosis has often been unnecessarily gloomy because the old person, having nowhere else to live, was accepted in the hospital as a long-term patient and given no active treatment. They would like to see mental-health services for old people as part of a comprehensive geriatric service based on a guidance centre. At the centre, which would be connected with a general or mental hospital, information about all the services for the elderly would be available. At first the patient could be investigated and perhaps treated in his own home or as an outpatient. Relatives would be free to consult the centre and old people would also be offered help with legal, social, or housing problems. The consultative health centre set up at Rutherglen [12] in 1952 seems to offer the kind of integrated service the committee have in mind and to be an encouraging, if unwitting, pilot scheme of their suggestions.

CEREBRAL EMBOLISM

THE effects of cerebral embolism are among the most dramatic and disastrous in medicine, and the permanent effects of a particular lesion are notoriously unpredictable at the time of onset. Recently cardiac surgery may have increased the immediate incidence by promoting embolism at or just after operation, but it has certainly reduced the remote incidence in rheumatic heart-disease, so that the age-group affected by cerebral embolism is becoming older.

In assessing the treatment of this condition results must be evaluated with great care and some statistical discipline, particularly if any individual treatment may worsen the patient's condition. Early workers in America, among whom Wright and McDevitt [13] were prominent, showed convincingly that the incidence of cerebral embolic phenomena was significantly reduced for long periods in patients receiving anticoagulant therapy. This work is now widely accepted by both cardiologists and thoracic surgeons in this country, but medical opinion is still divided over the use of anticoagulant therapy in the immediate treatment of the embolism itself. One reason for this is that Millikan and Whisnant and their colleagues [14] at the Mayo Clinic have shown that in animals anticoagulants may increase the severity of experimental hæmorrhagic infarcts.

The first attempt at a statistical analysis of the results of treatment in acute cerebral embolism was in 1957 when Carter [15] found in a four-year study of 60 patients that there was no significant difference in outcome between his control series and the group treated by repeated stellate block, but he also found that a significantly higher number of patients recovered when anticoagulants were given soon after the embolic episode.

A recent report by Wells [16] from New York describes his experience with 185 patients admitted to hospital from 1940 to 1958 with the diagnosis of cerebral embolism. He accepts only 82 of these as undoubted cases of embolism, and divides these into 29 patients treated with anticoagulants and 53 not so treated.

The 53 untreated patients had 63 separate cerebral embolic episodes: 33 were women, and the incidence was greatest in the age-group 40–60. Wells observed that 47% of these patients had sinus rhythm on admission, that the onset was most frequently during waking hours, and that headache was a feature of onset in 25% and convulsions in 12·5%. 25% of these patients died and another 35% had severe permanent neurological dysfunction. A mortality of 33% was recorded by Harris and Levine [17] and 50% by Carter.[15] As for prognosis Wells [16] concludes that convulsions, prolonged loss of consciousness, Cheyne-Stokes respiration, and a spreading lesion are bad signs, and that prognosis worsens with increasing age. Most physicians will agree that an elderly person with a large cerebral embolism does badly.

The treated group of 29 patients had 34 episodes: 13 were receiving anticoagulant therapy at the onset of the embolism and 16 started this treatment within forty-eight hours. In this group 6% died, a considerably lower mortality-rate, but 40% had severe permanent disability; so the results, as measured by death and disability together, were improved from 60% to 46% by anticoagulants —a difference that is not statistically significant. This compares with Carter's [15] figures of 66% dead or disabled in the untreated group and 31% in the treated group. It is perhaps doubtful whether the American groups can be accepted as strictly comparable, since they are numerically so different and the comparison is a historical one; but at least Wells has confirmed Carter's view that anticoagulant therapy does not appear to increase either mortality or morbidity in cerebral embolism. It is, however, a little disconcerting to observe that 13 out of the 29 treated patients were already receiving anticoagulants when the cerebral embolism occurred.

Neurological opinion in this country is naturally cautious and is still concerned about the dangers of this treatment. Brain [18] has said that after an ischæmic stroke there is an area of brain in which the capillaries are damaged, and that therefore it seems unwise to give anticoagulants within at least three weeks of an attack of cerebral infarction; and on the Continent this view is shared by de Morsier and Tissot.[19]

The value of anticoagulants in the immediate treatment of cerebral embolism has not been clearly established, although two reasonably well-controlled series have shown that this treatment seems to be effective. It also appears that the dangers of anticoagulants in acute cerebral embolism are not so great in practice as experiment and theory might suggest, and physicians interested in cardiology or neurology may feel that this treatment can now be given a fuller trial without risk.

11. Age and the Working Lives of Men. 1959. Pp. 67. 3s. (Obtainable from the Nuffield Foundation, Nuffield Lodge, Regent's Park, London, N.W.1.)
12. Anderson, W. F., Cowan, N. R. *Lancet*, 1955, ii, 239.
13. Wright, I. S., McDevitt, E. *Ann. intern. Med.* 1954, **41**, 682.
14. Moyes, P. D., Millikan, C. H., Wakim, K. G., Sayre, G. P., Whisnant, J. P. *Proc. Mayo Clin.* 1957, **32**, 124.
15. Carter, A. B. *Quart. J. Med.* 1957, **26**, 335.
16. Wells, C. E. *A.M.A. Arch. Neurol. Psychiat.* 1959, **81**, 667.
17. Harris, A. W., Levine, S. A. *Ann. intern. Med.* 1941, **15**, 637.
18. Brain, W. R. *Lancet*, 1957, ii, 857.
19. de Morsier, G., Tissot, R. *Rapp. Congr. franç. Méd.* 1957.

UNIFIED FORCES' MEDICAL SERVICE?

IN the past forty years amalgamation of the medical services of the Armed Forces has been repeatedly mooted and repeatedly rejected—notably by the Mond-Weir Committee after the 1914–18 war, by the Government in 1948,[1] and by the Waverley Committee in 1955.[2] When this committee's comprehensive survey was published it seemed that the issue, if not dead, would at least remain long dormant; but last year it was momentarily revived by the Ministry of Defence,[3] and now the Select Committee on Estimates [4] have breathed new life into it by declaring its support for amalgamation—or what they prefer to call integration. Rejecting some of the Waverley Committee's arguments, they point to two new factors justifying reconsideration of the proposal. The first is the evolution in the size, shape, and tasks of the Services, which by 1963 will be smaller and all-Regular. The second is the example of Canada, which since the start of this year has had a surgeon-general charged with the task of gradually unifying the three medical branches. The committee add, moreover, that "the alternative policy of coordination has not brought about the economies through rationalisation which it was intended by the Services that it should, nor is it certain that it will do so in the future".

The arguments for and against integration are set out briefly but fairly.

The advantages of a joint service would stem mainly from its greater size and scope. Thus doctors and nurses would gain wider clinical experience and enjoy better professional opportunities; there would be a pool of doctors, each attached to his own Service but available for duties in other Services, from which each Service could draw specialists, research-workers, or men with special experience; and from these two advantages would flow a third—namely, greater efficiency. Administratively, the number of doctors and civilians needed to run a joint medical service would, in the committee's view (but not, apparently, that of the Service Departments) be smaller, and consequently more senior doctors could be released for professional work; promotion prospects would be improved; and hospital facilities could be better deployed.

The considerations against integration (as the Waverley Committee indicated) include: (*a*) the specialised medical needs of each Service; (*b*) the differing tasks and functions, and so the differing organisation, of each Service; (*c*) the constitutional responsibility of each Service Minister for the health and efficiency of his Service, and the undesirability of his sharing this responsibility with the Minister of Defence; and (*d*) the loyalty of medical and dental officers to their own Service and the consequent esprit-de-corps of each medical branch.

The Select Committee (like the Waverley Committee before them) are not convinced that the establishment of a common organisation need be prevented by the specialised needs of each Service; and they point cogently to the example of the Royal Naval Medical Service, which undertakes the care not only of Naval personnel ashore and afloat but of Royal Marine personnel afloat and of Naval flying personnel ashore and afloat. As regards the differing tasks in the three Services, the committee claim that administration could be integrated (as in the Canadian scheme) without divorcing each branch from its parent Service. The Waverley Committee insisted that each Service Minister must of necessity retain responsibility for the health and efficiency of his Service, and that integration would inevitably involve division of this responsibility, adding that the Ministry of Defence was not organised to assume such an administrative task—a view eagerly endorsed by the Ministry itself in its evidence to the Select Committee. The committee conclude, perhaps rather lamely, "that further study should be given to methods under which the responsibility of Service Ministers for the health of their Service can be discharged under an integrated central administration". With regard to loyalty and esprit-de-corps, the committee are satisfied (as is the War Office) that these can be safeguarded; and it mentions particularly the continued wearing of different uniforms and the attachment of recruits to the Service of their choice.

In their investigation the committee found the attitude of the Service Departments "disappointingly inflexible". They gained the impression

"that integration is strongly opposed by the Service Departments, for differing reasons, and that there is such a pronounced bias against it as to make an impartial study on their part of the possibility of integration difficult of realisation. This was more obvious in the civilian than in the Service witnesses . . ."

The committee, for their part, concede that integration should proceed gradually and empirically, as in Canada; and they recommend, as a first step, free exchange of medical officers working in Service hospitals. But they are far from satisfied that the case for integration will receive a fair hearing by those who formulate policy. The responsibility for reviewing the principles on which the administration of such services as the medical branches is based rests with the Defence Administration Committee.

"Yet it was not denied by the Ministry of Defence witness that, of the members of this committee, 75 per cent, would have an ingrained bias against integration under the Minister of Defence because it would be taking something away from their own particular Service, while the remaining 25 per cent., those from the Ministry, would be biased against integration in so far as it involved them in administrative duties."

The committee suggest that the Ministry of Defence should seek independent advice on "the strategy of administrative rationalisation".

The case for unification, though strong—and certainly stronger than it was when the Waverley Committee was deliberating—is not unassailable, and the report falters notably when it considers the objection of divided Ministerial responsibility in a joint service. The report is likely to command more general agreement when it turns to coordination. Since the Waverley Committee reported there has been some progress (though in at least one important instance this was achieved by the intervention of the Treasury and the Ministry of Defence, and not by agreement among the Services); but such examples are all too few, and the mechanism for multiplying them is rusty or non-existent. To remedy this, the committee proposes that medical services coordinating committees be set up in the United Kingdom at Command level; and that the central Medical Services Coordinating Committee be enlarged by the addition of two or three civilians. This recommendation was made by the Waverley Committee but was rejected by the Services for reasons which do not impress the Select Committee. The members of the present coordinating committee, they say,

"are all Government servants, Service or civilian, and excepting the Treasury and Ministry of Health representatives, are

1. Statement on Defence. Cmd. 7327. H.M. Stationery Office, 1948.
2. Forces Medical and Dental Services Committee: First Report. H.M. Stationery Office, 1956.
3. Central Organisation for Defence. Cmnd. 476. H.M. Stationery Office, 1958.
4. Fourth Report from the Select Committee on Estimates. Session 1958–59. Medical Services of the Armed Forces. H.M. Stationery Office. 1959. Pp. 257. 14s.

all connected with or are members of the defence Services. Inevitably, they must lack something of the impartiality which civilian members would bring to their deliberations. On professional matters, the Services maintain panels of consultants of the highest rank, whose advice they greatly value and whose services are continually in demand. Your Committee find it difficult to believe that the presence of professional men of such calibre on the Medical Services Co-ordinating Committee would be other than extremely valuable. Another aspect of the committee's work where their advice would be of great assistance is in the infusion of new concepts and ideas." The existing committee, "the only central organ of co-ordination", has in the past ten years reduced its meetings from sixteen to four a year, for a morning on each occasion; and the Standing Committee take "a serious view" of the shortcomings of the coordinating committee, which they would like to see replaced by a new and larger body.

This would consist of an independent chairman, not necessarily a doctor, from outside the public services, and two or three civilian doctors, together with the medical Director-Generals of the Services and the Chief Medical Officer of the Ministry of Health (as at present), and other members representing the Departments who would qualify by virtue of their experience of administration and finance. The committee would report to the Minister of Defence, who would be responsible for approving its recommendations, and if necessary obtaining Cabinet authority. The present medical advisory boards would be disbanded.

The Select Committee range over other topics—financial control of the medical services, Service hospitals, cooperation with the National Health Service, recruitment to the medical services, and Service dentists—but their section on coordination is by far the most telling. Here, it seems, some opportunities have been carefully neglected; and perhaps this is one of the occasions on which we should not cheerfully accept the old Service custom of turning a blind eye on disagreeable suggestions.

RESEARCH IN TUBERCULOSIS

THE National Tuberculosis Association of the U.S.A. has published an account of the development of its research activities, from the appointing of its first "permanent Committee on Research" in 1915 to the complex of grants-in-aid and fellowships of 1955.[1] It is an interesting story. For the first five years little money could be given for research; but after a survey of the position in 1920 the sum of 20,000 dollars was appropriated in the following year's budget to support four research projects. The grantees were William Snow Miller for a study of the anatomy of the lungs, Esmond R. Long for work on the growth and metabolism of the tubercle bacillus and the chemistry of tuberculin, Ernest L. Walker for a study of the therapeutic value of chaulmoogra oil in tuberculosis, and a committee headed by H. K. Pancoast for a study of standardisation of X-ray films with a view to establishing a policy for uniform interpretation of "normal chests" at different ages. The choice of these four projects shows a proper balance between fundamental scientific studies and those of immediate practical value; and the long list of work supported by the Association since then has the same characteristic. Of the 20,000 dollars appropriated in 1921 only 4579 were used. By 1954–55 the appropriation for research had risen to 260,203 dollars, of which all but about 4000 was expended. About the same time it was estimated that associations affiliated to the National Tuberculosis Association were also spending approximately 200,000 dollars a year in direct support of medical research. But the total expenditure of funds raised by voluntary contributions was probably quite a small proportion of the whole cost of tuberculosis research in the U.S.A. A survey in 1949 had shown that funds supplied by voluntary organisations formed only 3% of the total contributions to research, the largest coming from official health agencies (57%), followed by manufacturing firms with 33%.

Since 1947 the Committee on Medical Research has been a standing committee of the American Trudeau Society, which itself is the medical section of the National Tuberculosis Association. In Great Britain the structure is quite different; for the professional organisation, the British Tuberculosis Association, has no connection with the lay fund-raising and educational organisation, the National Association for the Prevention of Tuberculosis (now known as the Chest and Heart Association). Figures for the expenditure of funds—official, industrial, and voluntary—are not generally available in this country. It seems highly improbable, however, that the total would be as high per head of population as in the U.S.A. On the other hand much very valuable research is being carried out here. The chemotherapy and vaccination trials of the Medical Research Council are well known and highly regarded throughout the world; much useful laboratory research is carried out in university departments and elsewhere; and the British Tuberculosis Association, despite financial difficulties, has in the past ten years built up an efficient research organisation. The Research Committee of the British Tuberculosis Association has not the funds to make large grants-in-aid or to provide fellowships, nor does it (as does the American Trudeau Society) issue guidance on current problems. It operates not only as an advisory body but also as an active instrument of research, carrying out, through its subcommittees, cooperative studies made possible by the well-organised structure of the chest clinics and chest hospitals in this country. Its current programme, for instance, includes field studies of tuberculin tests for epidemiological use, therapeutic trials of chemotherapy and corticosteroids, investigations of vaccination with freeze-dried B.C.G. by the multiple-puncture method, a study of relapse in tuberculosis, newly launched therapeutic trials in chronic bronchitis, and, in collaboration with other organisations, vaccine trials in chronic bronchitis and chemotherapy trials in genital tuberculosis. In addition, it has a subcommittee dealing with requests from pharmaceutical firms for advice on and trial of new products. For a relatively small professional organisation with only ad-hoc official financial support and operating on a small budget, this is an impressive list.

The record of the National Tuberculosis Association in assisting medical research in the U.S.A. is one to be proud of. It is to be hoped that the present declining public and professional interest in tuberculosis, a symptom of which is the change of purpose and name of the National Association for the Prevention of Tuberculosis, will not be allowed to interfere with the initiation, prosecution, and financing of research in tuberculosis in favoured countries where, although the disease may be decreasing, there exist the necessary abilities, organisations, and money. It is interesting that there appears so far to have been no attempt to change the name of the British Tuberculosis Association or of its official journal—*Tubercle*.

1. Tuberculosis Medical Research: Historical Series No. 9. Virginia Cameron and Esmond R. Long. National Tuberculosis Association, New York. 1959. Pp. 325. $5.

Occasional Book

THE N.H.S.
ORIGINS, ACHIEVEMENTS, SHORTCOMINGS

"One cannot help feeling that in the process of adjusting the ideals of the Service to the old medical system, to post-war economic conditions and the exigencies of public administration, especially Treasury administration, the ideals themselves have receded more and more into the background and that some of the more important of them have indeed been lost sight of altogether."

Professor Eckstein, of Harvard, spent two years in England studying the National Health Service. His book[1] is clear and fair and reminds us of much we are forgetting. Also it demolishes some mistaken notions of the origins of the service—notions current not only abroad but sometimes at home.

ORIGINS

The N.H.S. embodies the classic socialist formula "To each according to his needs", and it is commonly considered an example of socialised medicine. Yet in a very real sense, Professor Eckstein says, its establishment marks a triumph of non-socialist over socialist ideas. To him it is evidence of the conversion of the Labour movement in this country to the institutions of bourgeois society. Whereas the early British socialists aimed at re-forming society, replacing its institutions with different and better ones, their successors have gradually shifted the emphasis: first to redistribution of society's benefits, and thence to rationalisation—to making the inherited institutional framework more efficient.

"Utilitarianism and the managerial aspects of Fabianism have gradually triumphed over utopian socialism, revolutionary socialism, and Christian socialism. . . . Not the least significant aspect of this process of change in socialist orientations is the growing acceptance by Labour of conservative nostrums for social improvement, that is to say, of ameliorative measures advocated by those who want to preserve the essentials of bourgeois society by remedying its accidental weaknesses."

The legislation of 1946 was the culmination of "a long preparatory process, a Health Service agitation, which had lasted almost three decades, and in which the socialists did not play in any sense the leading part". To attribute it to Labour egalitarianism is wide of the mark. Before 1948 the less well-to-do certainly did not get their "fair share" of medical services; but if the sole purpose of the N.H.S. had been to relieve people of paying doctors' bills there would have been precious little reason for enacting it. Legislation and philanthropy, in roughly equal degrees, had already made medical care accessible to the poor, and as a distributive measure the N.H.S. benefits the middle class much more than the working class.

But to regard it as a distributive measure is a vast over-simplification; for economic reasons were only secondary in its creation. "The British," Professor Eckstein explains to his American readers, "have a socialized medical service simply because of the deplorable state of the old medical system . . . It was apparent by 1946 that the condition-of-medicine question could not be solved within the boundaries of the old system. What was required, above all, was a source of finance which could reliably supply the immense funds required by a modern medical system and an administrative authority which could impose purpose and pattern on the chaotic medical accretions of the past. Both of these requirements could be met only by the national government."

BEFORE THE SERVICE

National Health Insurance, introduced in 1912, gave a large proportion of people at least a first line of defence against the financial and physical hazards of disease; but this scheme was doomed to failure from the moment when the power to give or withhold so many of its prospective benefits was entrusted to the "approved" insurance societies. Because of this concession to the voluntary system, benefits were distributed unfairly, unequally, and inadequately, at a high administrative cost; and the result by 1946 was an overwhelming sentiment against the insurance principle. Likewise the inequality between the medical services provided by different local authorities, many of which made only feeble use of their permissive legislative powers, was one of the reasons for deciding to have a national health service rather than a series of local ones.

Professor Eckstein's picture of "the condition of medicine" is indeed grim. We were short of beds and equipment. Social (mainly financial) selection deprived us of many of the doctors—especially specialists—whom we needed. Moreover neither the hospital beds nor the doctors were always in the places where they were most wanted. Whereas the effects of shortages and mal-distribution might have been alleviated by rational organisation, organisation was in fact irrational, especially in the hospitals.

Britain had no hospital "system" at all: "there were, at best, two badly coordinated hospital patterns, each consisting of a large number of equally poorly coordinated parts". The depression of the '30s had been followed by war: many of the public hospitals, starved of the money they needed for reconstruction, still looked very much like the workhouses they had formerly been, while "the shoestring budgeting of the voluntary hospitals meant a cumulative, unsatisfied hunger for rebuilding, expansion, and re-equipment which has not been appeased yet".

But the hospitals were not the only part of the system to have financial troubles.

"The medical profession was not too well off either; it also needed an increased supply of funds. There is a general tendency to picture medical incomes, both in Britain and elsewhere, in far too roseate terms."

In general practice the most pernicious effects of economic difficulties, in the long run, were "overwork and certain slovenly professional habits"; and for this and other reasons general practice was in the worst "clinical" shape of any of our medical services. In other countries, too, it has been in scientific crisis: the pressures making for its restriction to routine cases are immense. But the problem was worse than usual in Britain because of the vast predominance of single-handed practices.

"The professional isolation of the general practitioner is at once the most anomalous and the most easily remediable product of the spontaneous historical development of medicine." But "the British profession displayed an amazing resistance to internal organizational innovations prior to the Health Service. Most doctors seemed to work on the unjustifiable assumption that isolated practice is somehow intrinsic to medicine. . . . The only plausible explanation is that there is a taboo on group practice in the British professions in general."

1. The English Health Service: its Origins, Structure, and Achievements. By HARRY ECKSTEIN. With a foreword by James Howard Means, M.D. Cambridge, Mass.: Harvard University Press. London: Oxford University Press. 1959. Pp. 289. 30s.

The difficulties of British medicine were brought into shocking relief by the war—whose medical history " reads like an administrator's nightmare ". The war inevitably brought about the end of the old system, both by the shortcomings that it revealed and by the attitudes towards medical reform that it engendered.

FROM AGITATION TO LEGISLATION

One of the remarkable things about Labour's nationalisation measures, Professor Eckstein points out, is that most of them were enacted in response to Conservative-dominated investigating committees. In medicine, as in industry, the plea for better organisation often came most forcibly from the expert; and Professor Eckstein describes the Health Service Act as a " doctor's measure " much more than a " patient's measure ", creating a " doctor's service " much more than a " patient's service ".

The N.H.S. is very far removed from British socialism's classic image of an ideal medical system. Illness, the early socialists thought, was a product of social conditions, and to provide free medical services was to miss the heart of the matter. The function of a socialist society was to abolish disease; and medicine, as it was known, would simply disappear under the ministrations of the benevolently sanitary society. The Fabian socialists were immensely suspicious of the medical profession; and the Labour Party's declaration in 1934 in favour of a free medical service represented a late triumph of the socialist doctors (the Socialist Medical Association) over the socialist anti-doctors. The attitudes of British socialists have evolved gradually " from a desire to remake society so as to abolish disease altogether, to a desire to redistribute more equitably the fruits of medical treatment, to a desire to reorganize and strengthen a medical system felt to be more inefficient than inequitable ".

In the agitation for reform " the political Left played a major role; but, in this case perhaps more than any other, the Left was not alone in desiring change ".

Three remarkable reports had no less than complete medical reform as their aims:

Of these the *Dawson report* of 1920 [2] was perhaps the most radical—though there was scarcely a single " radical " on the officially appointed council over which Lord Dawson presided. The family doctor was still to be the core of the system, but he was to work in " primary health centres " visited regularly by specialists and connected with the " secondary health centres "—i.e., general hospitals extended both in size and in range of work. These two kinds of centre, with supplementary ones providing special services, were to be coordinated by unified local health authorities. (This plan preceded the organisation of the Socialist Medical Association by more than a decade.)

In its *General Medical Service for the Nation*, appearing first in 1930, the British Medical Association's *principles* were almost at one with those of the more radical reformers; and though it did not want a free medical service for everyone, and limited itself to short-term suggestions, it agreed that planned organisational change must be the major task in the next stage of medical development.

Thirdly, the *Medical Planning Commission* [3] in 1942 produced " the most remarkable plan for self-reform in the history of the British profession ". Though it preferred something less than a universal service and sought to preserve voluntary hospitals, it wanted " nothing less than a unified, centrally planned, public medical service based on a new system of general practice [from health centres], a regionalized hospital service, and governmental control either through the Ministry or a medical ' corporation ' ".

By 1942 the profession was beginning to agree with the programmes as well as the principles of the more ambitious reformers, and the B.M.A.'s representative body endorsed almost all the more important recommendations of the Medical Planning Commission. But up to now planning for medical reform had been predominantly a professional enterprise and a paper enterprise. As soon as the Government was seen to be willing, indeed anxious, to act without professional prodding, the doctors' reformist heat abruptly turned frigid.

" The profession was caught in an unenviable dilemma. It favored medical reform; it opposed, by reason and instinct, the intrusion of nonmedical organizations into medical affairs; but there could be no medical reform without such intrusion."

The effects of the Medical Planning Commission on the profession's attitude were perhaps as shortlived as they were intense; but its effects on Government planning were immense. Stimulated by the commission, by its experience of the Emergency Medical Services in the war, and by the Beveridge report (though this did little more than add impetus), the National Government went ahead.

When Mr. Aneurin Bevan became Minister of Health he offended the profession by refusing to admit that medical organisation was a matter for doctors to decide. He would take the profession's views into account, and he would negotiate over terms of service; but he would never negotiate over the organisation of the N.H.S. itself. Since medicine is a " mystery ", it was clearly undesirable to push through legislation unacceptable to the initiates; and there was a risk that the profession would refuse to work an unsatisfactory Act. On the other hand, to use the advice of interested groups is quite a different thing from giving them a virtual veto over legislation—a kind of constitutional power to grant or withhold assent to Acts of Parliament. Though much good will was dissipated by the Minister's high-handed behaviour, Professor Eckstein says:

" In retrospect, it seems clear that there was no alternative course of action open to Bevan. What was at stake was not only the speedy reform of the medical services themselves but the very status of Parliament as a legislature and the role of the Cabinet as an indivisible policymaking body."

OBJECTIVES

The war led to a new and stronger consciousness of community, and to a general assumption that future problems would be tackled with the same sort of collective effort as went into the war itself. Moreover, there were special reasons why the Government should try to make medical care (unlike most other things) accessible to every citizen:

" One is that the treatment of illness does not so much involve the distribution of a society's goods as the remedy of its incidental, in some cases deliberate, evils. There was a good deal of naïveté in the old Socialist belief that surgeries and hospitals would have no place in a properly organized society, but there was a greater measure of truth, and there still is, in their belief that the incidence of disease is closely related to social stratification. . . . The naïveté of Shaw has become apparent with a better understanding of the nature of disease. . . . But the old uneasiness of conscience which made the acquisitive society turn from the cathedral to the hospital for moral consolation still lingers, and so does much of the justification for it.

" Again, disease is not merely a product of social malorganization; it is itself a potent factor making for such malorganization. In a society which pays for its medical care as it pays for

2. Ministry of Health: Interim Report of Consultative Council on Medical and Allied Services. 1920.
3. Draft interim report of the Medical Planning Commission. *Brit. med. J.* 1942, i, 743.

its groceries nothing is more certain to produce swift impoverishment, to wipe out all the gains of thrift and to degrade without rhyme or reason. It is not at all strange, therefore, that even individualist societies should try collectively to mitigate the effects of so accidental a matter as physical incapacity."

In most countries medicine has always enjoyed special priority among the social services. And in Britain, Professor Eckstein says, " charity, compulsory insurance, a free national service—all were essentially similar responses to disease as a manifest social product and social liability, the differences between them being due to changes in the nature of medicine and the operative values of society ".

The immediate objectives of the new service were largely dictated by the state of affairs before the Act was passed. Generally speaking, the doctor's fee was not a serious barrier to getting treatment; and merely to make the existing pattern of services available free of charge was certainly not enough.

" From an economic standpoint the most pernicious barrier to treatment . . . was the inability of charity and the local authorities to shoulder the burden of financing an adequate range of services, and the inability of the system of professional training, especially specialist training, to turn out . . . an adequate supply of adequately trained practitioners. In short what was needed even more than the abolition of the doctor's bill was a healthy injection of funds into the treasuries of the hospitals and local authorities and into the doctors' own pockets, and the rational distribution of such funds among individuals, localities, and medical institutions."

The first objective, then, was to fill the gap left by the diminution of charity and local rates (they had diminished, at any rate, in relation to the cost of efficient modern medicine); but there were bound to be limits on the proportion of the national budget that could go to medical services. It was equally important to remedy the maldistribution of man-power resulting from overconcentration of services in certain areas; but any abrupt redistribution of medical personnel would be fiercely resisted by public and profession alike. In a sense, therefore, the most immediate objective of the service was to use the existing system as efficiently as possible—to reorganise and rationalise it.

Rationalisation in this context has three meanings. First, economical organisation—" the elimination of waste and duplication, the performance of medical functions where they are most suitably performed, and stretching existing personnel and facilities as far as possible by proper coordination and a proper distribution of workloads ". Secondly, the use of an organisational pattern well adapted to the requirements of modern medical practice. Thirdly, the creation of an organisation which is highly responsive to planning—which permits accurate quantitative calculations to be made, workable plans to be formulated, and those plans to be carried through.

To the three major operational objectives—adequate and rational financing of services, rational control over their distribution, and rationalisation in the other senses just outlined—must be added two others.

The first was the maintenance of an effective doctor-patient relationship. Though in a sense this is a negative objective, it is fundamental to achieving the positive aims of the scheme. Confidence in the practitioner is essential to effective practice.

" It is difficult to specify concretely just what an effective doctor-patient relationship is and on what factors it depends, and usually people who talk about it do not even try; but this very nebulousness of the relationship makes any interference in it seem all the more dangerous. . . . Some aspects of the relationship have become subject to medical ethics or public legislation "; but most of them " are the results of quite spontaneous functional adjustments to an extraordinarily tension-ridden role and, insofar as this is the case, their very existence is logically, but not necessarily correctly, associated with a spontaneous rather than an artificially organized practitioner-patient relationship. It was precisely this which made the profession so desperately wary of nonmedical organization, public or otherwise, and it is the possibility of unsettling the relationship, especially in view of its mysteriousness, by the intrusion of a third party into it which is the chief problem here."

Many doctors feared that the State would inevitably subject the practitioner to demands irrelevant to the clinical situation and potentially destructive of it: " demands for economy, for fitting patients into generalized classifications, for treatment along standardized lines, for an annoying amount of paperwork, and so on. The chief threat to medical practice in this respect was stereotyping—the gradual displacement of the spontaneous clinical relation by bureaucratic rules and standards . . ."

The second of the additional objectives was "democratic organisation "—i.e., administration of the service by bodies on which those who work in it, especially doctors, are represented in considerable numbers, plus the wide use of professional advisory machinery.

Nowhere did the Labour party carry this syndicalist ideal so far as in the N.H.S.—certainly not in the nationalised industries. One reason for this is that the dangers of bureaucratisation loomed unusually large in the service, and substantial participation by doctors in its administration was meant to prevent the more dangerous consequences that might flow from public control. Another was that the profession made such participation a condition of accepting the service.

Pointing out that nobody is really guaranteed a full range of medical services under the Act, Professor Eckstein describes its introductory statement of purpose as not only vague and pious but downright misleading. " Basically the Service stands or falls not on its ability to supply free medical services—that, after all, is not so difficult—but more of them, more efficiently, than did the old system, without significantly changing the doctor-patient relationship as it evolved in the old system."

ACHIEVEMENTS

The doctor-patient relationship could have deteriorated because patients made inordinate demands; because there were too few doctors to meet the new requirements; because doctors would not serve public patients as well as they serve private ones; or because bureaucracy intruded into the relationship, overburdening the doctor with paper-work and dictating to him on scientific matters. Professor Eckstein sees little sign that the public have abused the service. If some practitioners have been overworked it is not because of patients' demands or a shortage of doctors but because the maximum permitted list is too big. He is inclined to think that, because of the traditions and ethics of medicine, the quality of the doctor's services depends very little on whether or not the patient pays a fee. And, though the Minister of Health has immense and detailed powers over almost everything that goes on in the N.H.S., the Ministry " seems to have a decently limited view of its role in the Service ", and the sum total of official intervention in the actual clinical relationship is very small. " Although great stacks of memoranda are issued on every conceivable subject . . . most of them merely contain 'advisory directions', that is, suggestions to the agencies which may or may not be adopted."

Indeed the layman's invariable self-effacement as regards technique goes far beyond the clinical relationship. On political and administrative issues the British Medical Association has got its way with remarkable frequency, and much of the organisation of the service has been designed to satisfy the profession's administrative preferences. The powers of doctors in administration are entirely out of proportion to their numerical strength. In fact their participation does more than protect them against lay encroachments into clinical matters—it makes for considerable medical encroachments on decisions which may be considered purely administrative. "There is, then, no bureaucratic tyranny over the profession; if anything, the opposite seems to be the case." As for the complaint about paper-work, it "died out in England almost with the very birth of the Service".

Since, in Professor Eckstein's view, the doctor's bill was one of the least serious problems to be solved, free medical care is one of the N.H.S.'s least significant achievements. He attaches more importance to what has been done to rationalise the services—especially the hospitals:

"The boundary problem has disappeared; the association of hospitals in regional groups has permitted a more effective distribution of medical functions among institutions and a considerable rationalization of hospital administration; improvements have been carried out in medical record-keeping, stores and inventory systems, out-patient departments, accounting and cost-accounting."

Perhaps most striking has been the great improvement in the distribution of doctors, both in general practice and the specialties.

Undoubtedly the service has cost more than was expected, but the figures given in the Beveridge report and the Coalition white-paper, so often cited in this connection, "were, at best, stabs in the dark; moreover, they were intended for something much less than a fully comprehensive, free national health service". The exercise of public direction over medical services appears to have checked rather than stimulated increases in their costliness: the idea of a ceiling for expenditure has become almost a fixed principle of N.H.S. budgeting, and the result is that the service has been given a dwindling proportion of the national income.

"Americans . . . expend a significantly larger portion of their much greater wealth on medical services than do the British, even though there is nothing like a comprehensive free service in the United States. In 1950, 4·5 per cent of all British consumption expenditures went into medical care; the corresponding American figure was 5 per cent. In terms of personal income, these expenditures amounted to 3·7 per cent in Britain and 4·4 per cent in the United States. The British proportion has been steadily declining, while the American medical system has continued, by spontaneous adjustment, to draw at least its usual allocation from the national wealth."

The relatively low cost of the N.H.S., "enforced by the ruthless rationality of the national budgetary process", may be adjudged one of its greater virtues. But Professor Eckstein regards it "at best a doubtful blessing" in relation to the ideals the service is supposed to achieve.

SHORTCOMINGS

The N.H.S. has created some sort of order, imposed some pattern and purpose, on the wasteful and senseless chaos it inherited. It has improved many things and made nothing appreciably worse. "Still, when one recalls the visions of the founders . . . the record of disappointed hopes and missed opportunities makes rather dismal reading."

". . . most of its original objectives have not been realized, some hardly even approached. Is this only because of postwar conditions in England? Perhaps; but it is all too easy for the men who control the Service to appeal to the conditions in which they have had to operate as a universal excuse for every failure, and to reassure themselves by comparing every present fault with the greater faults of the past. The danger in this is that . . . the faults of the Service will persist even when the conditions responsible for them have vanished."

Professor Eckstein, whose study seems to have been completed several years ago, begins by considering the shortage of beds—a subject on which informed opinion has been changing. He is on firmer ground in discussing failures of coordination.

The service, he points out, is in three parts, "with only the Ministry to hold them together", and despite much advice and many liaison committees "no really unified administration exists at any point in the field".

"It is perhaps surprising that so important a matter should have been left so much to the whims of the agencies, but the belief that effective coordination is best achieved by spontaneous relationships in the field, by overlapping appointments, *ad hoc* contacts, and a mushroom growth of special committees, is typical of British administration in general."

Perhaps the most obviously harmful effect of the administrative separation of these three services has been a great deal of unnecessary pressure on hospitals.

But coordination is still faulty, Professor Eckstein holds, not only between the three parts of the N.H.S. but also within them; and he condemns the English separation of teaching from non-teaching hospitals.

The principal raison-d'être of the regional boards is hospital planning, yet almost all key hospitals are independent of their jurisdiction. Hospital planning is the function of two divided authorities, and all the old dreams about an integrated system of primary and secondary hospital centres, about central hospitals and satellite hospitals, have come to little. Mapping out the regions on the basis of the teaching hospitals has led both to an administrative fiction and to a cumbersome, sometimes pointless, pattern of administrative areas.

But, though serious problems in the organisation of hospitals still exist, they pale beside the problems of general practice.

"After all, little was wrong with the hospitals which more of them, coordinated planning, and a certain amount of up-grading could not cure. General practice, on the other hand, needed organizational revision from the bottom up. It posed by all odds the worst professional problems inherited by the Service; but, after five years, its difficulties, far from being solved, have only been aggravated. The Health Service has not created these difficulties. . . . But because of the imposition of Health Service demands on the pre-Health Service organization of practice, its problems have been relentlessly brought to a head."

As Professor Eckstein sees it, the crux of the difficulty is the failure of the N.H.S. to promote group practice on a large scale, and particularly its failure to provide more than a handful of health centres. Why did the Ministry rule out even a decent amount of experimentation with health centres? Clearly the Government had a change of heart on the centres, but he cannot find a convincing reason for its altered attitude.

"It is true that opinion in Britain has gradually veered from Health Centres to group practice among general practitioners as a substitute. But it should be obvious that, while mere group practice is as efficient as Health Centre practice from the practitioners' standpoint, it is not as useful from the standpoint of the Health Service. Above all, Health Centres, correctly used (not as the few existing Centres seem in fact to have been used), may make possible real coordination on the spot with related medical services, particularly those supplied by the local authorities, and thus may solve two enormous problems with a single means."

The health centres were envisaged as the principal means of coordinating and rationalising the non-institutional services, as the Dawson Committee had recommended: they were to be " the common ground for all the medical and allied services in their bearing upon one another". Because of the tripartite division of the N.H.S., and the need for coordination of work between general practitioners, the hospitals, and special services, this was very important indeed; and, in a memorandum sent out just before the N.H.S. started, the Ministry called the health centre its " key feature ". But even Mr. Bevan's promise to build a chain of experimental group-practice centres, as an alternative, was not fulfilled.

" The hope of 1948 that the Health Service would radically alter the condition of general practice has been disappointed; nor has any concerted effort been made to realize it. Because of the importance of general practice as the first line of medical defence and its deplorable condition before the Health Service, this must be reckoned as perhaps the greatest failure of the Service."

A SPENDING SPREE?

There are many good reasons for N.H.S. shortcomings other than mismanagement. The medical services had accumulated immense arrears in professional and other man-power, in grounds, buildings, and equipment, in maintenance, modernisation, and extension. While the inherited Services might be reorganised to fit the new pattern, the pattern itself had to be adjusted to fit the services. The new administrative structure could only be considerably less than ideal, and the old system had engendered loyalties and other attitudes which were bound to produce vexatious political pressures and frustrating personal relationships.

Moreover, the N.H.S. came into existence at a very unpropitious time, when shortages of materials, inflationary pressures, shortages of personnel, and the need to give first priority to industrial reconstruction and housing made it impossible to do many of the things known to be necessary. Above all, though the Treasury provided a more assured supply of funds than had donations and rates, it also brought certain irrelevant considerations to the finance of medical services.

" The health services were now wed, for better or worse, to the national budgetary process. In an inflationary period public spending simply had to be severely restricted. Moreover, the objective need for economy was buttressed by certain obvious political attitudes. . . . The Health Service had become, almost overnight, the chief claimant on civil expenditure and, along with this, the first target of any objective or emotionally felt need for economy on a national scale."

Shortages of materials were even more devastating than the budget ceiling, and capital outlay on the hospitals was considerably smaller even than in the depression years.

But already when Professor Eckstein wrote his report most of the financial and economic excuses, he believed, had ceased to apply; and he urges that the time has come when the original purpose of the N.H.S. should be resuscitated. That purpose was never to distribute medical services more fairly among economic classes but to provide *better* services to all.

It was " to make the teaching spirit pervade a vastly extended hospital system, to place general practice on a more modern footing, to coordinate the services in an economically and scientifically effective way and—above all—to inject into a medical system which has been starved for more than a generation a much larger supply of wealth. None of this has been done; only the distribution of the services has been significantly improved."

So perhaps it is high time " to let the Health Service go on a spending spree, instead of continuing to subject it to the miserly penny-pinching necessary in the immediate postwar period, provided, of course, that the money is used to approach the real objectives of the long Health Service agitation ".

* * *

The above summary may suffice to show that Professor Eckstein's comments, coming from an outside observer, can be of immense interest to those of us who have been living, and will go on living, with the N.H.S. But, long though it appears, it is no more than a summary; and the book is one that needs to be read in full before it is discussed—as discussed it must be.

Special Articles

PERCEPTUAL ISOLATION USING A SILENT ROOM

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MUCH evidence—both theoretical (Walter 1953) and clinical (Brain 1951)—suggests that continual sensory bombardment is necessary to the maintenance of consciousness, awareness of one's relationship to the environment, and intelligent adaptive behaviour.

A relatively recent development in psychiatry has been the study of the effects of reduced perceptual and sensory stimulation. To cut out all sensory input is obviously impracticable, but ingenious devices have been used to reduce it to a minimum.

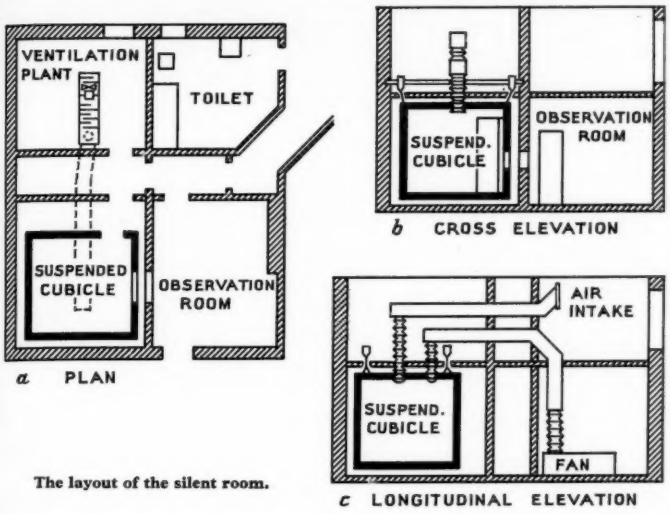
Early investigators at McGill University found definite effects after isolation, especially on psychological testing (Bexton et al. 1954); and many subsequent papers have described psychological sequelæ. The only exception is the carefully planned work by Vernon and Hoffman (1956) from Princeton University which failed to confirm the original findings of the McGill workers.

The means used for diminishing sensory input included tank-type respirators (Wexler et al. 1958), immersion in a tank of water kept at body temperature with air supplied through a mask (Lilly 1956), and an ordinary single hospital room, farthest from the centre of the ward and darkened by heavy curtains (Azima and Cramer-Azima 1956). It seems doubtful, however, whether any of these significantly reduce perceptual stimulation; and different experimental conditions might well account for the different findings. We have therefore tried to secure the most rigid conditions of isolation consistent with reasonable physical comfort.

Method

In selecting a suitable room for these investigations we felt that the layout and construction must enable us to compare our results with results obtained elsewhere, especially as regards the exact level of sound in the immediate vicinity of the subject. We decided that the ideal basis for such comparisons must approximate " perfect silence ": " white-sound " generators, which blind out extraneous noises, are unsatisfactory because of the wide differences in frequencies which penetrate different establishments.

Three rooms were chosen on the top floor of an isolated ward building; and the entire wall, ceiling, and floor were insulated with sound-absorbent material. In one of these rooms a massively insulated cubicle, measuring 9 ft. × 8 ft. 9 in. × 7 ft. 6 in., was constructed and suspended freely on four fine nylon cords



The layout of the silent room.

to minimise sound conduction through the building fabric (see figure).

A series of sound-proof doors on the approach corridor and between the various rooms was provided, as well as insulated glass observation panels between the observation room and the suspended cubicle.

A special ventilation plant was installed, great care being taken to exclude all sound from fan motors, incoming and extract air streams, or from outside. This was achieved by special silencers, ducting, and connection glands. Lighting and heating of both the hanging cubicle and the observation room could be varied from the observation room, thermostats taking care of the temperature. Plugs and wiring for tape-recorder or microphone were provided between the observation room and the suspended cubicle, and provision was made for electro-encephalographic recording.

The efficiency of the sound insulation was tested.

Measurements were made by Acoustical Investigation and Research Organisation Limited, London, at third-octave intervals, from 80 to 10,000 cycles per second, in accordance with British Standard 2750/1956 (" Recommendations for field and laboratory measurements of airborne and impact sound transmission in buildings "). A special oscillator was used as a noise source and a microphone fed the resulting sound levels to a third-octave spectrometer. This, in turn, was connected to a recorder on which a graphic sound spectron was produced and measured.

TABLE I

No.	Sex	Age	Total deprivation time (hours)	Reason for leaving	Percentile grade (progressive matrix)	M.M.Q. scale †
1	M	42	51·0	Anxiety + panic	1	14
2	M	52	25·40	Anxiety + somatic *	2	17
3	M	32	5·50	Panic	2	22
4	F	47	51·57	Anxiety + somatic	3	13
5	F	26	31·50	Anxiety	2	19
6	M	40	23·45	Anxiety + somatic	3	22
7	F	52	75·30	Anxiety	3	10
8	M	50	37·5	Anxiety	2	17
9	F	55	48·40	Anxiety + somatic	3	11
10	M	30	28·35	Anxiety	2	19
11	F	20	82·34	Anxiety	3	9
12	M	20	33·55	Anxiety	3	16
13	F	40	30·55	Anxiety + somatic	2	26
14	M	20	25·25	Anxiety + somatic	2	19
15	F	22	5·55	Panic	2	25
16	F	30	28·10	Panic	2	18
17	F	44	92·20	Anxiety + panic	3	8
18	M	26	32·40	Anxiety	2	19
19	F	25	43·40	Anxiety	3	10
20	F	27	37·50	Anxiety	3	12

* Anxiety plus physical symptoms—aches and pains, muscle cramps, headaches, &c.
† Maudsley Medical Questionnaire scale (Eysenck 1947)—a scale of personality factors which discriminate between normal and neurotic. The higher numbers show a progressive trend towards the neurotic scale.

The results showed that, whereas the uninsulated layout with all doors closed had a sound-pressure-level difference of from 30 decibels at 80 cycles per second to 40 decibels at 10,000 cycles per second, the insulated layout had a difference level rising to as high as 82 decibels at 10,000 cycles.

Volunteers in this room could either rest on a bed (made up of ' Dunlopillo ' mattresses) or walk about. This eliminated muscle cramp and other physical discomfort resulting from immobility. Their eyes were covered with translucent goggles which cut out patterned vision. Their hands and arms were enclosed in padded fur gauntlets: these and cotton gloves effectively reduced tactile sensation and were much more comfortable than cardboard cylinders which caused muscle aching and discomfort in the elbow region. Heavy woollen socks were pulled over the feet.

The volunteers were unaware of being under observation through the one-way screen. Four times a day they were visited, and the hours were slightly varied so as to test their time appreciation. They were then quickly questioned about themselves, the gauntlets and eye-pieces were removed, and a meal was set before them. They ate in isolation. With the goggles on again they were then led to a toilet and back. The whole operation of disturbance was timed from beginning to end: it constituted what we called " partial " sensory deprivation (e.g., in the case of the woman whose total deprivation-time was 92 hours 20 minutes, deprivation was partial for 4 hours 40 minutes). The volunteers were left in the cubicle for as long as they could stand it: all knew that they could terminate the experiment at any time by telling the observer or letting themselves out of the room.

TABLE II

—	Average age (years)	Average total deprivation (hours)
Men	34·6	29·24
Women	33·5	48·70

Volunteers were recruited from nurses and hospital workers. They were promised an amount of paid " time off " equal to that spent in the room.

All were asked to fill in the Maudsley Medical Questionnaire and all carried out a Raven's Progressive Matrix.

Results

20 volunteers were tested (11 women and 9 men)—table I shows how long they were able to remain in the room and their reason for leaving it. This information is also correlated with the percentile grade on the Progressive Matrix and the Maudsley Medical Questionnaire.

One of the unexpected results was that women in general seemed to last longer than men (table II).

Twelve aspects of mentation were studied, inquiries being made each time the subject was visited.

1. *Thinking* became disordered in all the 18 volunteers who stayed in for any length of time. The main difficulty was concentration: in many volunteers it was completely lost. In 2 this loss progressed to complete disorganisation of thought—a " jumble of thoughts with no rhyme or reason ". In 12 it was the disordered thinking that produced fear and panic: a man described it as " I thought this meant I was going mad "

2. *Affect.*—Only 1 volunteer had a definite depressive reaction with crying; but all had anxiety and often panic attacks, either early in the test or, more usually, terminally. Unbearable anxiety, tension, or panic attacks was the main cause for giving up.

3. *Psychomotor activity.*—18 volunteers became agitated and

restless, both subjectively and objectively; and this was the forerunner of the thinking difficulties in 9. At least 4 found that their agitation could be better controlled lying on the bed than walking about.

4. *Time.*—This was usually overestimated by between half an hour and three hours. 7 subjects at first persistently underestimated by half to one hour, but towards the end of the experiment all were overestimating.

5. *Body-image disturbance.*—7 volunteers experienced this, mostly towards the end of their time. The head and arms were the parts involved; and the phenomena were described as " my head is like a spinning cone going away from my body ", or " my arm is like a ton-weight and feels fatter than my body ".

6. *Somatic signs and symptoms.*—Great efforts were made to eliminate these. The room was constructed so that the volunteer was not cramped; and by giving the subjects fur gauntlets instead of rigid cardboard cuffs we helped to eliminate complaints which would have been irrelevant to the experiment. In 3 cases such complaints were a manifestation of anxiety-tension, though the volunteers—looking for a more reputable " escape " than anxiety or panic—denied this.

7. *Irritability.*—A special effort was made to watch for irritability. Azima et al. (1956) had suggested that during such isolation libidinal drives were frustrated, which provoked aggression; and that this in turn was repressed and introverted " causing a split in the ego ". They also found a negative association between overt aggression and changes in body scheme. Only 2 of our volunteers expressed irritability or became aggressive: the first was a heavy smoker after he had been unable to smoke for twelve hours, the second a man whose reaction to any form of stress had always been loss of temper, irritability, and aggression.

8. *Sleep.*—Except the 2 volunteers who left the room in a state of anxiety after six hours, all slept more at the beginning. This seemed a perfect illustration of Kleitman's (1929) theory that sleep is induced by a decrease in afferent impulses from the sensorium, producing a reversible inactivity of the highest cortical centres. There was a strong positive correlation between those who slept most and those who lasted longest in the room.

9. *Dreams* were invariable in those who slept for any length of time, and in 5 they attained a nightmare quality when tension and anxiety were growing. Suffocation, drowning, killing people, &c., were features of the nightmares.

10. *Appetite.*—Except in the 2 volunteers who left early, appetite was always good in the early stages. It then became progressively poorer until meals were being left almost untouched. " Lack of fresh air and exercise " or " headaches " or " feeling sick " were some of the reasons advanced.

11. *Delusions.*—In no volunteer were definite delusional ideas established. In 2 there was a suggestion of a paranoid state—a feeling that they were being neglected or forgotten—but these ideas did not persist.

12. *Hallucinations.*—A woman who stayed in the room for over 70 hours maintained that towards the end when she was having difficulty in thinking, she saw " tree trunks waving about "; but these may well have been illusionary phenomena brought about by sweat running down the goggles.

Discussion

Published results of this type of experimentation can be divided into two groups. Some workers, like Bexton et al. (1954) and Goldberger and Holt (1958), have described well-marked sequelæ to sensory deprivation, including disturbances of thinking, imagery, and time appreciation, and delusional and hallucinatory phenomena. Others, such as Vernon and Hoffman (1956) found virtually no sequelæ. Most of this work can be criticised on the ground that the conditions of sensory deprivation, particularly the degree of silence, have not been measured. The experiments of Vernon and Hoffman are especially interesting because their chamber was a " floating room " which was measured to an 80-decibel sound loss—conditions comparable to ours.

Their volunteers were 4 college men from Princeton University who went into the chamber under conditions of sensory deprivation (goggles, cardboard cuffs, &c.) for a set period of forty-eight hours. Vernon and Hoffman found no delusional or hallucinatory phenomena; and they accounted for those reported by Bexton et al. (1954) as probably caused by repetitious masking noise or by amorphous visual stimuli. The Princeton workers encountered no thinking anomalies either, perhaps because their volunteers were few and highly selected and because the isolation period was set in advance.

Our 2 volunteers who left the room after five hours were anxiety-prone worrying personalities. The first obtained a score of 18 and the second a score of 20 on the Maudsley Medical Questionnaire, which tends to confirm their neurotic tendencies. Indeed, if Eysenck's conception of the dysthymic personality is accepted (Eysenck 1947), there is a close correlation between this group and inability to stay in a room for any unusual length of time. The findings shown in table I lend support to the clinical impression that the placid and calm person with an intelligence level at or somewhat below average is best able to deal with this kind of sensory deprivation.

Our observations and records outline a fairly clear-cut chain of events. At first most volunteers show a tendency to sleep, some for an unduly long time. Then follows a period of growing agitation, tension, and restlessness. Disturbed thinking, particularly obsessional, occurs about this stage; and most subjects experience panic which makes them leave the room. But some of our volunteers, even when perspiring profusely, with trembling limbs, dry mouth, and tachycardia, still clung to the conventional dislike of " anything psychological " and maintained that their reason for giving up had been backache, headache, or some other " socially approved " symptom. A 20-year-old girl showed none of the usual premonitory signs (e.g., restlessness) until about the 80th hour: then, very quickly, she became restless and developed the idea that she was locked in the room. This, she knew, was untrue, but the idea persisted and increased in intensity together with a feeling of distress. This miniature and experimental obsessive-ruminative state developed over an hour or so; and the ensuing anxiety and panic was only relieved when she pressed the plunger to let herself out.

We feel that in general these results fall half way between the excessive symptoms recorded by Goldberger and Holt (1958) and the entirely negative findings of Vernon and Hoffman (1956). Since, however, our work has been carried out in a standardised silent room, it will be possible for others to perform similar tests under comparable conditions, preferably with test assessments of various psychological functions which, so far, we have been unable to do.

The experimental situation itself can be used for many and varied investigations. For example, 2 volunteers who were complaining of disturbed, disjointed, and obsessive thinking (and whom one confidently expected to retire very soon) were able to go on for another thirty-six and twenty-five hours after carrying out a progressive matrix. It seemed as though the discipline required to marshal thoughts and to concentrate had re-established their normal thinking pattern.

We believe that sensory deprivation is an important psychiatric tool. It has been used to explain mental abnormalities in various types of illness (Leiderman et al. 1958). Senile nocturnal delirium has also been ascribed to a diminished efficiency of the sensory apparatus and impaired ability to adapt to new sensory stimuli (Cameron 1941).

Azima and Cramer (1956) have used this type of deprivation in the therapy of mentally ill patients. They con-

ceived a disorganisation/reorganisation process which, they felt, had helped some of their patients. Their work has been criticised as confusing " description . . . with theory " (*British Medical Journal* 1956); but they did suggest a dynamic psychological hypothesis—that isolation frustrates libidinal drives and causes a narcissistic injury which provokes aggression; and that this aggression is subsequently repressed and introverted causing a split in the ego. We were unable either to confirm or to refute this formulation.

We have not yet been able to investigate the physiological effects of sensory deprivation, with the possible exception adding support to Kleitman's (1929) theory that a decrease in sensory stimulation is a prerequisite for going to sleep. Azima and Cramer (1956) have discussed an organic or physiological hypothesis, based on the work of Magoun (1950), Jasper (1949), and others on the integrative function of the reticular system and its relation to cortical areas by a diffuse projection system. Isolation, resulting from a diminished sensory input, might cause a disorganisation of somatognosia and changes in body scheme. This theory has the merit of fitting the work of Magoun and his collaborators into a coherent system, which may well be susceptible to experimental verification.

We have encountered no post-isolation phenomena. 2 men and 2 women were alleged to be " quieter and more easy to get on with " for about a week after the experiment, but the subjects themselves strenuously denied this. A woman volunteer became ill about two weeks later, and the diagnosis was said to be " nervous debility "; but we do not believe that this illness had any connection with our experiment.

Summary

A " silent room " was designed, constructed, and standardised up to a mean sound-pressure-level difference of 80 decibels. 20 volunteers spent varying periods—from 5 hours and 50 minutes to 92 hours and 20 minutes—in this room, under conditions of partial and complete sensory deprivation.

Apart from many individual reactions, a general sequence of events was observed: increasing sleep, followed by restlessness and agitation, followed by thinking difficulties, and finally succeeded by panic. No post-isolation phenomena were seen.

In this volunteer group (11 women and 9 men) the women lasted better than the men; but this may not be the general rule.

There is scope for further research in this field, especially to explain the changes observed: and its relevance to everyday medical work is mentioned.

We would like to thank the Hospital Management Committee for their imaginative support and encouragement and all the volunteers who assisted us. Particular thanks are due to Assistant Matron Dunderdale and Sisters Hargreaves, Hetherington, and Masters for their unflagging help and supervision of the volunteers whilst in the room.

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In England Now

A Running Commentary by Peripatetic Correspondents

ONCE we had accepted the idea, there was little controversy about the closure of our hospital and a minimum of angry letters in the local paper from outraged citizens. That was about a year ago, and in a short time the hospital, to the outside observer, seemed to go back to normal. But underneath there were many spoken and unspoken fears—redundancy, loss of pay and pension, loss of status, and fear that the other hospital to which we were being transferred wouldn't be quite the same.

By the day the first patients were due to depart some who saw little future for themselves had gone to other jobs and the jigsaw of fitting two hospital staffs together had been at least partly completed. The personal problem of adapting ourselves to the new environment remained. Then one day after a two-week transitional period, when we didn't quite know where we belonged, we were suddenly all in our new homes. Two days later we all returned for a final visit to the empty shell of what had been our hospital. There were farewell speeches, prizes were distributed to nurses, we all sat down to tea, and then suddenly it was all over and the hospital just a memory. To me the memory will be of out-of-date buildings in a beautiful setting of bluebell woods approached through a fine avenue of chestnuts. It is only too easy to get nostalgic over all this, and it is as well to remind oneself that the landscape was rather lost on people who found they had to come to a bluebell wood on the top of a hill, three miles out of the nearest town, to have their tonsils out. To them the bluebells were not so blue and the avenue of chestnuts was only too long and steep.

* * *

Annie has been coming to the surgery for years with a new complaint every time. In my early days I used to hunt for the causes, but for some years I have tended, I fear, to treat her rather lightheartedly.

She came in on Friday evening with a story of burning water and a bottle to prove it. To support my intended reassurance I tested some for albumin over the bunsen burner. There was a roar and a spurt of flame and I dropped the lot, shocked and singed. " My God, Annie, you've really got something wrong this time." " Oh, Doctor, I'm terribly sorry. I've given you the wrong bottle. That must be my new shampoo."

I have today ordered some of these tablets for urine testing. I am told they are simpler and cleaner, but it's their safety that really attracts me.

* * *

I threw down the *Radio Times* with a disappointed sigh the other evening and suddenly decided to take in twopenn'orth of Tarzan at the local cinema. I recalled my youthful thrills and looked forward pleasurably, if a trifle shamefacedly, to recapturing them. The first disillusionment came with the first appearance of the hero: " This fellow's deformed," I thought, regarding his bulging triangular torso with a cold, adult, and professional eye. I comforted myself with the chimpanzee, remembering how he always stole the picture. I had failed to reckon with changing times and tastes, because the chimp after two brief glimpses did not appear again. The new Tarzan had a more handsome face than the old, but I never found out whether his swimming was as spectacular because he did so little of it; he swung through the branches once only (or it may have been twice) and his girl was a sophisticated hussy, not nearly as helpless and bedazzled as she should have been. She did however take fantastic risks in order to steal some penicillin for him from the enemy camp.

What really disturbed me was the ingenious succession of violent and ugly deaths which seemed to constitute the entire film, and the apparent relish with which man's inhumanity to man was portrayed. The noble savage won through, of course, as of old; but I emerged shaking slightly and thanking my stars that I had made the decision to see Tarzan after the children were safely in bed.

* * *

The B.B.C. may seem unduly timorous to restrict the use of a song about the Stone of Destiny to selected programmes. But after all they must know best where the thistle pricks, and they could claim some support from the reaction of The Church to the Kirk (and vice versa). Consider, for instance, what happens when a patient is admitted to hospital:

In England: "What is your religion?"
"Church of Scotland."
"Oh, I see—Presbyterian."
In Scotland: "What is your religion?"
"Church of England."
"Oh, I see—Episcopalian."

And there is a nasty weed that in Scotland is called bishop weed and in England ground elder.

* * *

My fellow peripatetic who suggests that to compare a fæcolith in size to an American golf ball indicates an obsessional neurosis, entirely misses the point. The gentleman with the St. Andrews qualification from Dundee is a true scientist, for the American golf ball is 1·68 in. in diameter as opposed to 1·62 in. for the ball used in Britain.

The inference is obvious. If the fæcolith had been 0·06 in. smaller, it must surely have been passed and so avoided an obstruction.

* * *

"When I was at high school," said the surgeon as he sewed the graft on my nose, "I took an aptitude test, and because of the way I handled the forceps they said I should be a surgeon."

"Ah, but did they have any controls?" asked his assistant.

"Well, one of my brothers took the tests, and they said he had no mathematical aptitude at all, and should never have anything to do with mathematics in any form."

"What happened to him?"

"He majored in maths in college, passed with honours, and is now an actuary in one of the biggest insurance firms."

"That seems to cancel out—one success, one failure."

"Then there's my other brother. He took the tests, and they said he just wasn't college material, and should never consider going to university."

Through the drapes that covered my mouth I muttered sarcastically, "And what is he a professor of?"

"How did you know he was a professor?" asked the surgeon testily.

* * *

DON'T CROCUM, LOCUM

(With apologies to Ogden Nash)

If there is one thing calculated to make you a cynic
It's the way the patients look at you whenever you start a minute late at the clinic.
It matters not to them—wrapped up as they are in their imaginary lesions—
That by the end of the morning your trousers will be practically grown to the seat with adhesions;
No. They've paid their National Insurance
And it's up to the doctor to have what it takes in the matter of endurance;
So what care they if he's driven mad or gets delirium tremens
Provided he can always lend an ear to anybody on his bemens?
Please, why is there always someone who has diabetes
But who hasn't got the sense to know where both his feet is
And such a liar that you've no way of telling if he's on the verge of coma
Or suffering in the throes of insulinoma?
Why are you always just about to set off for a well-earned break
When you're urgently called to visit someone with myxœdema, scabies, effort syndrome, and an indescribable ache?
And why is it, when you've just got home again,
Your bell will ring and you will learn that grannie's got a pain?
I suppose the fact is
It takes all sorts to make a world and even more to make a practice,
And unless you watch yourself for paranoia
G.P. will soon destroia.

Letters to the Editor

GENERAL PRACTICE

SIR,—Dr. Godber's paper and your leading article of August 29 raise several important points to which insufficient attention has been paid hitherto. May I offer a single-handed country doctor's reactions to some of these?

Medicine becomes increasingly complex and hence increasingly specialised. To be fully up to date with any subject a man must limit himself to one system, one method of diagnosis, one age-group, or one method of treatment. Diagnosis has become more precise, and treatment more effective and more dangerous. Both depend on special techniques and experience available only in hospital. The centre of gravity of medical practice is shifting from the doctor's surgery to the hospital outpatient department. In my practice in 1957, out of 2187 patients on the list 62·8% consulted me during the year. Of these 18% were referred to the outpatient department and 6% were admitted to hospital as emergencies.

What is the general practitioner's place to be in this advance? The more the patient is divided between the specialists the more important is the general practitioner's role, since he alone stands for the whole man, in sickness and in health, from the cradle to the grave. He is the final common path by which the achievements of medicine are brought to the patient, yet he cannot be fully conversant with them, nor, as things are at present, has he at his command the necessary tools of the trade. In my experience Dr. Godber is unduly optimistic when he states that in a great many places general practitioners have direct access to pathological and radiological facilities. In this area chest X-rays have recently been made directly available, but barium meals and other special investigations are not; as a result the outpatient departments are crowded with patients sent up, not for the consultants' opinions, but for radiological investigations which the general practitioner was taught as a student to rely upon.

Medical practice has been divided into watertight compartments and the pressing problem for the future is how to break these down. Communications are inadequate. Much intimate detail is lost in the letters that pass between general practitioner and consultant, and each has much to learn from the other and contribute to the patient's welfare by meeting at consultation. Can this be achieved?

I believe that it can because I have seen it happening.

I had the good fortune to work for a time at a cottage hospital in the country; it had twenty-five beds, an outpatient department, an operating-theatre, an X-ray room with a part-time radiographer, and a small clinical side-room. The hospital is staffed by the practitioners of the neighbourhood. At regular intervals, monthly or fortnightly, it is visited by consultants from the teaching hospital twenty miles away and cases are seen by general practitioners and consultants together. The family doctors are provided with the modern methods of diagnosis the results of which are available at the consultation. The best and most intelligent use of consultations can be made under such circumstances, both can learn from the other, and the patient does not lose contact with his family doctor as can so easily happen in a busy outpatient department.

This situation is perhaps utopian and not of universal application, but it suggests certain important principles. To do their work properly general practitioners must be in a position to order all the investigations which as students they were taught to use. The purpose of consultation is for two men to meet and share their special

training and experience to the patient's advantage. The consultant's function is to give an opinion and not to order an investigation. The general practitioner's contribution will be drawn from his knowledge of the patient's background and personality; it is he who will decide that a woman's symptoms are explained not by an electrocardiogram on the borderline of normality but by a mother-in-law on the borderline of insanity.

Since many of his problems must be sent to hospital the general practitioner should follow them there. Hospital outpatient departments are overcrowded and (in the provinces anyway) understaffed. Much of the outpatient work could well be done by G.P.s working as clinical assistants.

To do this G.P.s must have more time; so long as doctors are expected as a matter of course to be overtired and rushed off their feet, so long will the watertight compartments remain sealed. We do not expect a 40-hour week, but a maximum list of 2500 would be the first step. We need more time, more incentive to use instruments other than the fountain-pen, and more understanding of each other's difficulties; for when the doctors fall out it is the patient who suffers.

Buckinghamshire. R. P. C. HANDFIELD-JONES.

SIR,—General practice is a constant source of discussion inside the medical profession, and all would be interested in reading the views of Dr. Godber (Aug. 29). They appeared to me to cover most of the points that are raised, but to omit the one which is essential to the happy solution of the problems involved. This is that the quality of work of the general practitioner and his relationship with his colleagues in hospitals or public-health services can be placed on a proper footing only when the atmosphere in which they work accepts and encourages the conception of a team of medical men and women directly concerned with the total health problems of a community. A long time ago in its draft interim report the Medical Planning Commission of the British Medical Association suggested that the future basis of medicine would be the recognition of the collective responsibility of all the doctors in a community for all the health problems of every citizen in that community.

A great many of the arguments about consultation between practitioner and specialist, about whether midwifery is a domiciliary or a hospital problem, about the question of whether general practitioners can have any place in a salaried hospital service, resolve themselves when the doctors concerned become aware that they are not in competition and that they are not conflicting elements but parts of a complex yet in reality single service.

Dr. Godber made a very kind reference to our experience in this area in giving an open access and domiciliary laboratory service, but this is only part of an effort to build up a free exchange of views and information which has many facets. We have in the Kingston area every type of variation of the theme of general-practitioner hospital including a small G.P. maternity unit. Our group medical advisory committee has specialists, general practitioners, and county medical officers as members; the B.M.A. meetings are held in the main hospital, and we in the laboratory also run monthly clinicopathological conferences which are very popular with G.P.s and hospital personnel alike. There is constant daily exchange between consultant staff both over domiciliary visits and over patients in the smaller hospitals. Without suggesting that the picture is complete or entirely satisfactory we can claim there is a great deal of understanding of each other's problems which makes the whole question of consultation a very much more simple one. From the laboratory side, for example, we may sometimes do a domiciliary visit which calls for little more than a written report to the G.P., but on the other hand we may receive a postal specimen which calls for immediate consultation with the doctor concerned.

It is this close daily interlinking which raises the standard of medicine practised by the G.P.s; but I hasten to add which forces up the standard of the service given by the hospital. A noticeable feature is the effect on these services of the advent of younger and more scientifically equipped practitioners. In this area we are handling many, many more patients than ever before, and this is at least partly due to the fact that the hospital can count on its G.P.s both to receive patients home from hospital much earlier than formerly and to keep patients at home even if they require fairly elaborate laboratory investigation and control.

It will be of interest to mention that we have in mind to add to this interlinking a medical club which will not only strengthen the professional links but will add social connections which should cement the feeling I have tried to indicate of working as a team.

Kingston Hospital, Surrey. D. STARK MURRAY.

ROLE OF THE PÆDIATRICIAN IN MENTAL ILLNESS

SIR,—Fortunately we are not all pædiatric pterodactyls. Many pædiatricians are adapting to the changing environment of medical practice—an environment in which physical disorders are dwindling and emotional disorders increasing in importance. Pædiatrics is evolving faster than almost any other subspecies of Medicine; but to encourage the evolutionary process exclusively in the direction advocated by Dr. Tizard and his co-authors (Aug. 29) would be putting all our eggs in one rather unsubstantial basket.

After much that is thoughtful and timely in their paper they state that "a personal analysis may in the future become a necessary or desirable part of training for *most* [my italics] family or pædiatric practitioners". They commit pædiatrics to a theory which has been seriously criticised; Eysenck, for example, attacks it not only for inconsistency but also because it does not generate testable deductions and is in consequence a trespasser in the realm of science. Opinions as to the value of psychoanalysis, whether as a means of studying emotional development or as a method of therapy, differ widely. To claim for it exclusive rights would call for indisputable evidence. Where is the evidence?

At the present time it seems reasonable to suggest that alternative methods should be encouraged, not least because they are likely to prove less time-consuming and more practicable. Some are already being explored by those who, like your contributors, are trying to equip themselves to deal with the many children referred to pædiatric clinics on account of disturbances which are not primarily physical. I hope that your contributors' article will bring them into the open, so that all methods may be critically compared and the best features of each adopted. In the development of the New Pædiatrics (to use a trans-Atlantic term) we need further exploration, not in one but in many dimensions of the pædiatric pansophy.

I disagree emphatically with the view expressed that, when parents come asking how to manage or feed their children, family doctors and pædiatricians should not give advice (though I would prefer to "offer guidance"). Certainly they should—who else? But, without limitation to any one school of thought, they should have prepared themselves by learning about children.

Bristol. JOHN APLEY.

SIR,—Some of us are rather forced to give inexpert advice on pædiatric emotional problems, to say nothing of

feeding difficulties, and have read with envy of the timeless sympathetic silences, the *dolce far niente*, of the Paddington Green approach. But I cannot help wondering whether any one of the authors would have written any of this if he had ever been involved for, say, a fortnight in what has been called working pædiatrics.

Royal Berkshire Hospital, Reading. J. J. KEMPTON.

SIR,—Dr. Tizard and his colleagues have stated well the present problem of the pædiatrician and his "major preoccupation". Although their speculations may be controversial their paper demonstrates the need felt by pædiatricians to know more about the children brought to them with bodily symptoms for which no physical cause can be found. And this need is reflected in the growing number of "groups" of pædiatricians meeting regularly with psychiatrists to discuss such case-material.

In his day-to-day work the pædiatrician may try to confine himself comfortably to organic disease, but in the process he sees many children whose illnesses offer an uncomfortable challenge: the ubiquitous child who won't eat, the screaming baby, the infant ideal in all respects except for his head-banging, and of course anxious parents with a child who is physically or mentally handicapped. Advice and reassurance are most tempting; they save time, and the doctor feels he has served his patient well. Sometimes they may appear to be effective, but so often the situation remains unchanged.

The pædiatrician in this changing setting has to learn a new approach, for the traditional "question-and-answer type of history-taking is valueless". Dr. Clyne (Sept. 5) is undoubtedly right to emphasise the "willingness to recognise and understand" and the need to "experiment and research". In practice this must be the first stage, and pari passu "he must provide a setting in which a parent can talk". The interview situation is all-important and necessitates the greatest endeavour, for it entails allocating time and the real feeling in the doctor that he is no longer the "expert" but a person who will attempt to work out with the patient what is afoot. These are easier said than done, for time is precious and to become an equal with a patient involves considerable maturity.

Once the pædiatrician, and for that matter the general practitioner and the local-authority medical officer, give themselves this opportunity they will be designing a new experience with rich rewards in the art and skill of human healing.

London, W.1. DAVID MORRIS.

EXAMINATION BEFORE ADOPTION

SIR,—The protest made by Dr. Black (Aug. 29) against a Wassermann reaction in infants for adoption is premature as syphilis is not yet absent from our country. Nor does a negative serological test of the mother during pregnancy ensure a healthy child.

For example, I tested one woman repeatedly throughout pregnancy, as she had been treated for gonorrhœa, but she was infected with syphilis by coitus with a foreign sailor less than a week before confinement, and she never had a positive W.R. Her baby was infected with syphilis, and was a candidate for adoption. Another woman had treatment for syphilis during pregnancy but disappeared before the course was completed. Her baby appeared healthy and the mother had a negative W.R., but the child had syphilis.

It is easy to obtain blood for testing by making a small superficial incision in the heel of the infant; I find a sterile new razor-blade excellent for the purpose. It is easy to collect 3–5 ml. blood in less than five minutes, and no special skill or equipment is required. In cases of difficulty of interpretation of serological results a venereologist will be pleased to cooperate with the practitioner.

Inherited syphilis is rapidly being removed from this country, and it would seem unfortunate to give up now any precaution. The adopting parents appreciate the certainty of absence of syphilis. It is only by continuing to take every possible precaution that we can detect the occasional and unsuspected case of syphilis. It is well worth doing many "negative" tests to ensure the detection of an occasional "positive".

Royal Infirmary, Edinburgh. ROBERT LEES.

PSYCHOSIS AND ADDICTION TO PHENMETRAZINE

SIR,—In 1955 a German observer reported that no signs of habituation had been observed among 60 patients treated with phenmetrazine ('Preludin') for up to a year.[1] All other stimulant or sedative drugs at first reported to be non-habit-forming have sooner or later been found to lead to habit formation or addiction, and preludin is no exception. Cases of excessive consumption of preludin, occasionally followed by the development of psychotic features, as reported by Dr. Evans (Aug. 22), seem by no means rare. Over the past two years we have seen quite a few of these, among both men and women, mostly unstable personalities, some of whom had in the past or at the same time also taken other drugs or alcohol to excess.

Generally they had started taking the drug for slimming, having been introduced to it by their doctor or by friends. They had taken it for up to two years and the maximum daily dosage was 100 tablets (2·5 g.), the (claimed) maximum dose at one time being 60 tablets (1·5 g.). All these patients had started with 1–2 tablets but increased the amount rapidly. To start with, most of these patients had felt very well whilst "under the influence" of the drug—"full of tremendous energy", "bursting over with ideas", "never ceasing to talk", and seeming to need little sleep. Some reported that "time did not seem to matter" or "went by in a flash". Those who had also taken amphetamine estimated that they required about 2 preludin tablets (50 mg.) for every 1 amphetamine tablet (5 mg.) in order to obtain a similar effect.

When the effect of the drug began to wear off these people experienced a let-down feeling and felt the need for "topping up". They felt "miserable" or "weak" and depressed, and even had crying spells. There was a definite craving for further tablets, one woman attacking her husband physically when he refused to let her have money to buy a further supply.

Those in whom the drug led to psychotic symptoms gradually began to feel that people were looking at them or talking about them, and some developed definite paranoid delusions and hallucinations. In some there was severe general deterioration of behaviour and self-neglect. The psychotic symptoms as a rule subsided fairly rapidly on withdrawal of the drug without evidence of physical abstinence symptoms. Dr. M. H. B. Joyce (personal communication), who referred some of these patients to us, noted the appearance of visual hallucinations in a young woman on the third day after sudden withdrawal; she had taken up to 80 tablets (2 g.) per day for two years without a history of hallucinations. With one doubtful exception there was no history of psychotic episodes prior to taking preludin in any of these patients.

At present carbromal preparations and preludin seem to hold first and second places in popularity among those who abuse unrestricted drugs, and one still comes across barbiturate and amphetamine addicts and habitués. As in the case of alcoholics, treatment should not consist in merely withholding the drug but should include attempts at long-term control. Group psychotherapy seems to be a suitable medium. It might be preferable to form a group exclusively comprising addicts to such drugs; but in the

1. von Bohm, E. *Med. Klin.* 1955, **50**, 1951.

absence of a sufficiently large number at any one time we have, over the past eighteen months, included these patients in a group consisting in the main of people with drinking problems. A little time and a few sessions seemed to be needed by these drug addicts for overcoming their initial resistance and their feeling of being "quite different" from the drinkers, but sooner or later most of them began to discover much common ground and participated freely and eagerly in the discussions. However, three of our female preludin "addicts" all left hospital within 10 days after admission before the "exposure" could "take", all saying they had now learnt their lesson and "never again" would they take preludin. Two of them relapsed within a few days and were readmitted, only to take their discharge again a few days later. But that an unsatisfactory result is not necessarily the outcome of the treatment of preludin "addiction" is shown by the example of the patient reported two and a half years ago [2] who, apart from a minor relapse, has kept off drink and drugs completely and has made a successful re-entry into an exacting and responsible profession.

St. Bernard's Hospital,
Southall, Middlesex. M. M. GLATT.

THE INJURED MINER

SIR,—I was interested in your note (Aug. 22) about the model coal face which has been constructed in Edinburgh. The last sentence is not entirely accurate as the Northumberland Miners Rehabilitation Centre at Hartford Hall, Northumberland, which is under the National Health Service, has a similar model coal face which was opened in May, 1950. To date 3150 patients have been treated at it, with very successful results.

Newcastle Regional Hospital Board, Newcastle upon Tyne. JAMES A. MCKEON
Assistant senior administrative medical officer.

DIMINISHED RESPONSIBILITY

SIR,—Dr. Maddison's most interesting lecture (Aug. 15) reminds one of a curious anomaly.

When a man becomes bankrupt he may be required to undergo an examination. He may be unable to "meet" his creditors financially, but he must nevertheless meet them, or their representatives, personally. It is demanded of him not only that he shall account for his accounts, but that he shall also explain how his conduct of his affairs contributed to the difficulties in which he finds himself. He is expected to be "accountable" for his actions.

In a criminal action, the convicted person may be asked if he has anything to say before sentence is pronounced; he may previously have made a "statement"; he may or may not have appeared in the witness-box: but there is no routine procedure for his being called to account for his behaviour, explain his actions, or be examined concerning these.

Such a procedure might be regarded as open to objection on various grounds—that the opportunity might be used as a platform for abuse, falsehood, exhibitionism, or propaganda, or that the accused might refuse to cooperate or be mute: but the response (whatever it might be) to what would amount to a test situation could be carefully noted, and even borne in mind in deciding appropriate sentence. A more valid and practical objection might be that of time.

But surely society in general, if not the injured party in particular, has a right, in addition to that of punishment and/or redress, to an explanation from the wrongdoer. It is more than likely that valuable information concerning offenders might be obtained in this way; and the possible deterrent value of convicted persons being called to account for their actions and having to undergo an examination, whether public or panel, is not to be ignored.

Liverpool. S. BARTON HALL.

2. Glatt, M. M. *Brit. med. J.* 1957, i, 461.

PREGNANCY COMPLICATIONS AND THE CHILD

SIR,—Your leading article [1] discussing some of our work was on the whole thorough and fair in its judgments: but a few statements in it constrain me to write in an attempt to clear the record.

It was stated that our work and that of others on the possible relationship of dietary inadequacies to prematurity and complications of pregnancy as precursors of prenatal brain damage was not yet fully convincing because "the diet of the village woman in Bengal contains a fraction of the protein in the diet of the most heat-exhausted American; and yet such observations as have been made among the less well-nourished peoples have included no record of an especially large incidence of epilepsy, palsy, or mental defect". I would appreciate references to such studies since I have been unable to find any. In view of the difficulty in even securing birth and death records, epidemiologic investigations of morbidity prevalence in underdeveloped countries understandably are quite rare. In addition, the well-known extremely low mean birth-weight of the Bengal child as well as the high infant death-rate would lead one to suspect that brain damage may not be infrequent. Birth-weight, apart from gestational age, has been found to be related to infant morbidity and mortality. Grossly brain-damaged children would also be expected to have a high mortality-rate during and after the neonatal period particularly in deprived areas. There is a growing body of evidence in many investigations other than ours and too numerous to discuss here that would lead me to believe that your leader may be doing a disservice to Bengal and other undernourished women by intimating that good diet is unimportant as far as their pregnancies and offspring are concerned.

You also quote Penfield as indicating that cerebral damage may result from postnatal infection and difficult labour. We can only agree with the former possibility although it must be relatively infrequent. As for the latter, in all the conditions we studied when the cases with complicated pregnancies and premature deliveries were removed we found no difference in dystocia and obstetric operations between cases and controls. More recent pathological investigation in our laboratories suggests that it is usually the brain predisposed by prematurity, prenatal œdema, and/or anoxia which is injured by the parturitional forces common to all deliveries. Professor Penfield had stated previously that immaturity apparently played a role in producing damage.

You state that our figures suggest that "perhaps 1 case of epilepsy in about 10 is associated with prenatal complications". For a number of statistical and research design considerations I would submit that our data cannot be used for this determination. The best that can be done with the data is to determine statistically significant associations and not incidence. It is similarly not possible to state with certainty that "most pregnancy complications are without harmful effect". For instance, on longitudinal study we found that fully half the prematures weighing under 1500 g. were seriously impaired.[2]

Some question was raised as to the propriety of accepting the 5% level of significance although it was generously conceded that the summation of the study results and the graded effect of maternal state "should not be lightly dismissed". However, you apparently accept uncritically the findings of Creamer on 94 children of toxæmic pregnancies when compared to 74 control children chosen in some undescribed fashion. Creamer had lost 25% of his original population and used, as his dependent variable of development, *reported* statements of

1. *Lancet*, 1959, i, 924.
2. Knobloch, H., Rider, R., Harper, P., Pasamanick, B. *J. Amer. med. Ass.* 1956, **161**, 581.

sitting, standing, and walking—notoriously unreliable indicators of intellectual functioning. He did report higher prematurity and stillbirth rates but the total number involved was so small that nothing could be done with the data.

Carter's study of 219 congenital defects was also quoted as contrary evidence since no association was found with seasonal incidence, previous abortions, or maternal conditions in pregnancy. Since congenital malformations are determined quite early in pregnancy it is unlikely that such relatively late appearing abnormalities as toxæmia or third-trimester bleeding would be causally involved. Such careful workers as Record and McKeown have found associations with previous abortions.[3] In any event seasonal incidence would be almost impossible to test when the small number of defects were distributed among 72 months, although Carter writes that he did find a " suggestive difference ".

Finally, the accelerated motor behaviour we found in Negroes in early studies is no longer present. In our last study of almost 1000 infants we no longer find any differences in this area of functioning.[4] Apparently norms for the modern child require alteration.

You quote us correctly as saying that the findings must be interpreted cautiously; the hypotheses advanced have not been definitively validated. I would maintain, however, that, in any scientific review, evidence on both sides should be equally critically weighed.

Columbus, Ohio, U.S.A. BENJAMIN PASAMANICK.

*** We should have been wiser to speak negatively rather than positively. What we meant was that doctors working in Bengal villages, and other places where many of the population are undernourished, have not drawn special attention to an abnormal prevalence of epilepsy, palsy, or mental defect. If we are wrong about this, and a higher prevalence is generally recognised, we, like Professor Pasamanick, would be glad to have references. We certainly do not think that nutrition in pregnancy is unimportant to the offspring.—ED. L.

CHINCHILLAS

SIR,—We were interested to see the advertisement for chinchillas in your issue of May 2. It is hard to understand how anyone can afford to try breeding them unless they sell for a few pounds per pair. Long experience in America proved that each pair produced less than one offspring on the average per year. This one had an ultimate value for fur of about $16. Many were worthless because they chose their own fur as part of the vegetarian diet.

Some of those who found very negative financial returns in this business gave their entire stock of animals and equipment to some of us doing research. Possibly this will happen on your side of the Atlantic and this unique species will readily contribute in advancing medical science.

Some of the characteristics of the species are (1) the long gestation period of 111 days in an animal the size of the common white rat; (2) the ease with which this species acquires atherosclerosis when fed small amounts of cholesterol; (3) the long life-span of this species compared with the rat (we have one over 7 years old); (4) the fondness of these animals for a diet of dried bread and hay; (5) the mystery of the composition of the urine and fæces of this species which makes it an odourless animal; (6) the rat-like tendons in the tails of the animals which are especially useful for studying the ageing of this tissue; and (7) the ability of this species to utilise about 50% of the fibre in its diet while the ordinary rabbit with the same form of gastrointestinal tract can only utilise 30%. This suggests differences in the microflora of intestinal tracts that appear alike. When maintained upon ordinary commercial rabbit feed in the form of pellets the urine of the chinchilla may be very clear while that of a rabbit looks like milk.

Cornell University, Ithaca, New York. CLIVE M. MCCAY.

3. Record, I. R. G., McKeown, T. *Brit. J. soc. Med.* 1949, **3**, 183.
4. Knobloch, H., Pasamanick, B. *in* Social Aspects of Psychiatry (edited by B. Pasamanick and P. Knapp); p. 123. Washington, D.C., 1959.

TREATMENT OF RINGWORM OF THE SCALP

SIR,—I have used the following treatment on many patients with success.

The hair should be plucked manually or clipped. Wash well with soap, dry, and apply over the infected area cautiously a fresh preparation of " 100-volumes " hydrogen peroxide, taking care to apply it *only* on or around the area of the scalp affected. Following that I applied a sulphonamide ointment (' Inotyol '), as an emollient. Usually one, or at most two, such applications lead to a complete cure and regrowth of normal hair after a few days. The only disadvantage is that this method is painful, and previous sedation of the patient is advisable.

French Hospital, San Francisco. HENRY CHAKER.

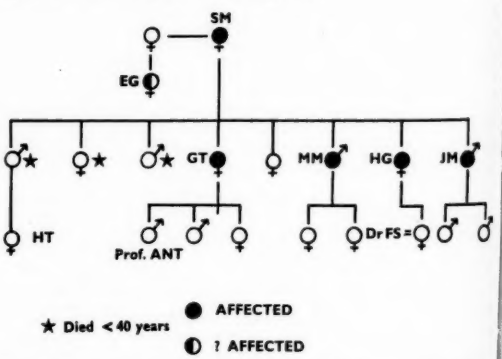
THE FAMILY POUCH

SIR,—This letter concerns an unusual family history of pharyngeal pouch.

On May 9, 1958, Mrs. HG, a bright and intelligent lady of 82, was seen in the outpatient department of St. Bartholomew's Hospital, complaining of difficulty in swallowing. She first noticed this six months before. Food seemed to stick in her throat, and she had the sensation of an obstacle. The difficulty in swallowing was worse with solid food, and she had to take liquids to help it down. There had been some regurgitation of food after meals, and she now had to eat her food minced up fine and take a long time over her meals. She had no gurgling on pressing on the throat, no nocturnal cough, and no appreciable loss of weight. There was nothing relevant in the past history.

She suspected her trouble was due to the " family condition "—namely, pharyngeal pouch. Several members of her family had similar symptoms which had been proved to be due to this condition. A barium swallow subsequently showed a small pharyngeal pouch. The cricopharyngeal sphincter was dilated by Mr. F. C. W. Capps through a pharyngoscope under general anæsthesia on July 4, 1958, with relief of her symptoms.

We have been investigating her family history and have prepared the family tree (see figure).



Her mother, Mrs. SM, was the first known member of the family to have a pouch. It showed itself when she was about 70 years old, and her daughter, Mrs. HG, recalls that it caused her to eat so slowly and with such loud gurgling noises that she had her main meal sent in to her in the sitting-room. She died at 89. Mrs. SM had 8 children, 5 of whom lived beyond 40. Of these 5, 4 developed pharyngeal pouches, when they were between the ages of 60 and 70 years.

The eldest affected sibling, Mrs. GT, developed her pouch whilst in South Africa. She refused operation, and died aged 75. The next affected member, Mr. MM, also had no operative treatment, and had considerable dysphagia before he died aged 81. The remaining affected member in this generation, Mr. JM, was successfully operated on by Mr. J. Heselson of Cape Town for removal of his pouch. He died at the age of 80.

Finally, Mrs. SM had a sister whose child, Mrs. EG, is reported to have suffered from the same condition, but I have no confirmation of this from a doctor.

None of the children in the third generation have, so far, developed a pouch, but only one of them, Mrs. HT, is yet of an age where symptoms are likely to show themselves. There is a doctor in the family who confirms the facts.

Dunhill [1] described a patient he treated whose brother, father, and grandfather were similarly affected; and he quoted Dinsmore as reporting 2 brothers with the condition. Bjork [2] described 3 sisters, all operated upon by himself for pharyngeal pouch, who developed symptoms at 67, 67, and 46 years respectively. Their mother also had symptoms suggestive of this condition from the age of 57 until her death at the age of 77. Bjork states that Vinson, in his monograph on diseases of the œsophagus, mentions that Spark had diagnosed the condition in 4 members of the same family in two generations.

I wish to thank Mr. F. C. W. Capps for permission to publish the details of the case he treated, and for the interest he has taken in this account. Prof. A. N. T. has been extremely helpful in contacting members of the family and in kindly providing the details of the family tree. Dr. F. S. and other members of the family have also been most helpful.

Department of Otolaryngology,
Manchester Royal Infirmary. R. F. McNAB JONES.

DETECTING LUNG CANCER

SIR,—In your editorial on this subject (July 4) you give a very fair appraisal of lung-cancer case-finding by mass radiography. You rightly encourage further evaluation of this as a case-finding method and at the same time raise some doubts as to its real practicality.

There is one further point in evaluating the end-results from mass radiography—particularly of asymptomatic persons—as compared with the end-results from the treatment of patients with clinically manifest disease. This has to do with the fact that a case-finding screening procedure when used in a population for the first time is determining prevalence of disease that can be identified by the case-finding procedure, and not incidence. The distribution of "kinds" of cases in terms of rate of growth, and (probably) prognosis after therapy, might be quite different for such prevalent cases as compared with previous experience with symptomatic (incident) cases. Perhaps this may be best illustrated from the example I have given previously [3]:

"... A second and unavoidable bias is the fact that slower progressing disease accumulates disproportionately among prevalent cases as compared to incident cases. For example, let us assume for a specific cancer site (the lung, for example) that cases occur annually at an equal rate that could have been found by a screening method six months, one year, and two years before becoming symptomatic. These three growth-rate types are occurring in the ratio 1 : 1 : 1. An initial screening procedure would find these cases in the ratio of 1 : 2 : 4 ...

"The bias of disproportionate accumulation of slowly progressing disease is of more serious concern in considering prognostic advantage of cases identified in an initial screening. Continuing with the example just given, presume the 5-year survival of these three chronology types is 0, 5, and 20 percent, for an over-all average of 8·3 percent. The initially-screened cases would have a 5-year survival of almost 13 percent—an apparent but fictitious advantage. Prognostic advantage for cases found by a screening procedure, to be compared with those diagnosed symptomatically, then, must be determined on the cases found in the rescreenings of the same population."

Field Investigations and
Development Branch,
National Cancer Institute,
2151, Berkeley Way,
Berkeley, California. JOHN E. DUNN, JR.

SELECTION AT CELLULAR LEVEL AND THE ECOLOGY OF TUMOURS

SIR,—Dr. Loxton asks, in his letter last week, whether I suppose that cell variation is Lamarckian, and I would reply that that part of inheritance which is transmitted by the cytoplasm is partly Lamarckian.

My view amounts in effect to a personal inability to accept that the epigenetic landscape is entirely intracellular, but I have the impression that that is somewhat at variance with the original conception developed in Waddington's series of essays. When a so-called organiser tissue is transplanted to a new site in the embryo it induces a differentiation of cells which then out-select the ones which would normally have occupied that site. It is quite clear that an extracellular factor is involved and the change must be Lamarckian, but I would myself suppose that the change was purely cytoplasmic and did not affect the nuclear inheritance at all. Dr. Loxton asks me whether I would regard the change as a mutation: I think that the answer is that the word mutation should be restricted to changes which affect the nuclear heritage, because I consider cytoplasmic changes to be facultative and reversible. On the question of virus I retain an open mind but would not quibble with Dr. Loxton's own view that the significance of virus is limited and particular rather than general.

In my earlier letter (Aug. 29) I had deliberately avoided reference to the controversies which have vexed the evolutionists during a century and a half and which are still smouldering with an intensity which I find disconcerting. If, however, this question of Lamarck is to be raised I admit that I have reasoned myself into a position from which the whole of the orthodox conception of biology appears in new perspective. Basic to the whole matter is the suggestion that nuclear inheritance is Mendelian and Darwinian, while cytoplasmic inheritance is partly independent of the nucleus and is Lamarckian. In the days of the great evolutionary controversy, when the theory of natural selection was being hotly defended from those who would introduce the taint of Lamarckism, the evolutionist was entirely unprepared to admit that genetic change could be any other than invariably random. In his own province the evolutionist was armed with the theory of natural selection, which effectively met and disposed of the enormous improbabilities associated with randomness, but that theory depended upon the competition and differential survival of variants with different genetic constitutions. Because the cell-community was genetically uniform the evolutionist was unable to concede that it could possibly provide a basis for the operation of selection as between cells. The cytologist was thus saddled with all the improbabilities demanded in defence of natural selection but was denied access to the mechanism which could dispose of those improbabilities. The problem of cell-differentiation was rendered impossible of solution and has remained so.

If one concedes that an element of cellular inheritance is cytoplasmic and Lamarckian, the whole picture appears in completely changed perspective. Differentiation is explained almost in one stroke, but infinitely more important from the present point of view is the fact that the cell-community emerges as a mixed population of variant cells competing under "natural-selection conditions" in an environment which they maintain in a state which approaches almost incredibly closely to the theoretical equilibrium environment which

1. Dunhill, T. *Brit. J. Surg.* 1950, **37**, 404.
2. Bjork, H. *Acta Otolaryng.* 1952, **42**, 202.
3. *J. chron. Dis.* 1955, **2**, 457.

is central to the science of ecology. The ecologist is entirely familiar with the equilibrium environment which supports its maximum life-potential of races whose demands are mutually compatible, and he is well aware that this state of ecological harmony not infrequently breaks down, with the result that a plague population arises. The ecologist has a whole series of laws relating to such occurrences which are in fact, as one might say, his stock-in-trade. Surely the tumour is no more and no less than a perfectly ordinary plague-population in miniature?

I venture the opinion that if these matters were seriously examined by a panel of discerning experts in biochemistry and animal-ecology the findings would quite possibly be enormously fruitful to both patient and physician. I am doubtful that this subject has ever been approached from quite that point of view.

Colchester, Essex. MICHAEL FROST.

PROGRESSIVE PATIENT CARE

SIR,—Give a dog a bad name and hang it. Give a dog a new name, like Progressive Patient Care,[1] and what happens? It may be the last word from the United States, but to me it has a much more homely sound. In fact, the resemblance to the sanatorium in which I have spent most of my working life is overpowering. There is the same immediate postoperative surgical unit; the same intensive nursing unit shared by postoperative cases at a later stage and the more acute medical admissions; and then there are the units for semiambulant and ambulant patients, where the emphasis is very definitely on getting well rather than being ill.

However, this is not an institution for progressive patient care, but a sanatorium, and as that has become a bad name I suppose we shall inevitably be closed down in the near future. It will be some consolation that the ideals of patient-treatment and rehabilitation which some of us have striven to maintain have taken a new lease of life.

Cheshire Joint Sanatorium,
Market Drayton, Salop. A. CLARK PENMAN.

BILIARY CIRRHOSIS LIPOPROTEIN

SIR,—A few years ago we noticed that the serum of a patient with biliary cirrhosis which was perfectly clear when separated became grossly turbid after freezing.[2] Subsequently we examined the effect of freezing and thawing on the turbidity of many sera, and found that the majority of jaundiced sera are notably clear and remain so after freezing overnight, but a few become moderately or grossly turbid. Such sera were found to have high cholesterol and very high phospholipid contents. They almost all come from patients with biliary or cholangiolitic cirrhosis.

We have found that the turbidity arises from the decomposition of an abnormal β-lipoprotein very rich in phospholipid, and this is probably the same lipoprotein as that investigated by Ahrens and Kunkel,[3] by Russ et al.,[4] and by Furman and Conrad.[5] None of these workers, however, mentions instability to freezing.

We feel that this decomposition must have been noticed many times, but has not been sufficiently publicised; we know of no reference to it except a passing mention by Dr. Discombe [6] in his recent comprehensive account of flocculation tests. Yet it would seem to afford an extremely simple method of detecting a phase of liver disease, and might occasionally be of help in diagnosis or prognosis.

We should like to hear from others who have observed this effect, particularly concerning the diagnosis, and would welcome any information on references in the literature.

North Middlesex Hospital,
London, N.18. W. G. DANGERFIELD
EUNICE HURWORTH.

1. *Lancet*, Aug. 29, 1959, p. 223.
2. Dangerfield, W. G. *Proc. R. Soc. Med.* 1956, **49**, 1065.
3. Ahrens, E. H., Kunkel, H. G. *J. clin. Invest.* 1949, **28**, 1575.
4. Russ, E., Rayment, J., Barr, D. *ibid.* 1956, **35**, 133.
5. Furman, R. M., Conrad, L. L. *ibid.* 1957, **56**, 713.
6. Discombe, G. *Lancet*, 1959, i, 1007.

BOOKS OR TEXTBOOKS?

SIR,—Your editorial of Aug. 29 suggests unhappy experience of the teaching of pathology. How often must the pathologist point out that pathology is the science of disease and that the study of morbid anatomy is only *one* of its approaches to the elucidation of its problems. Nor can one agree that it is morbid anatomy which has given "organic medicine and its exposition a rigidity no longer compatible with our times". Even the approach through morbid anatomy and histology can be dynamic. To write of pathology as a "static edifice" is to admit a complete ignorance of the potentiality and of the reality of the subject. How much of modern endocrinology stems from the physiopathological observations of the pathologist! Surely too it is only when biochemical or biophysical findings are incorporated into the broad picture of the pathology of the disease process that the glimmer of understanding is first seen. In an age of ultra-specialists the pathologist must remain the *fons et origo* from whom the surgeon, the physician, the biochemist, and the pharmacologist must seek the balanced philosophy of the problems of disease.

Department of Pathology,
The Queen's University of Belfast. J. HENRY BIGGART.

"INCURABLY OF UNSOUND MIND" REDEFINED

SIR,—You report (Aug. 22) the judgment of Mr. Justice Phillimore in a case where a woman successfully petitioned, on the ground of "incurable insanity", for divorce from a husband who had prospects of early discharge from hospital. The judge held (and your Legal Correspondent approved his argument) that despite the man's hope of leaving hospital he must still be held to be incurably insane, because he would be able to live only under very sheltered conditions. This case reveals a most unsatisfactory state of the law.

Firstly, it is anomalous that the woman, whose husband is likely to be discharged at the end of the year, can obtain relief by divorce if she petitions now but not if she petitions next year—even if her husband's state of mind remains essentially the same; for the law still requires that the partner shall have been under continuous care for the past 5 years. It is surely wrong that the timing of the petition should be crucial, independent of the prognosis of the spouse.

Secondly, it is anomalous that this woman can obtain divorce from a husband who, it is agreed, will soon be fit enough to live at home, whereas relief is denied to another woman whose husband, even if now suffering a mental handicap of equal severity and chronicity, has not in the past been ill enough to need 5 years in hospital. Apparently the granting of divorce may depend upon past history, rather than upon present state and future prospects.

It seems in the light of Mr. Justice Phillimore's judgment that a spouse is entitled to divorce not merely on the ground of permanent separation from an insane partner, but also if that partner suffers from mental incapacity of only moderate degree—provided illness has been worse in the past. It is one thing to pronounce a marriage ended

because cohabitation and normal relationships are permanently ended. It is quite another thing to release a person from the marriage contract when he or she is faced with a burden which many of us would not consider intolerable.

High Wycombe, Bucks. GEOFFREY ROSE.

*** Our Legal Correspondent writes as follows.—ED. L.

The whole subject of divorce for insanity bristles with difficulties. It is the only ground for divorce which does not involve some form of misconduct by the respondent. If there is to be divorce on the ground of insanity, it is desirable that it should be subject to definite conditions. The imposition of such conditions always involves the risk of anomalies, but it seems reasonable that time should elapse before the divorce petition is presented. Parliament has fixed this period at five years. If the respondent has been under care and attention throughout that period, a divorce will be granted if it can be shown that there is no prospect of the respondent returning to normal life. The prognosis remains the crucial question. The effect of Mr. Justice Phillimore's judgment is that the petitioner is not to be refused a divorce merely because there is some prospect of a partial cure which would enable the respondent to return home to live an artificial existence protected from the normal incidents and problems of life—an existence which his Lordship likened to that of the bedridden patient. Is Dr. Rose quite fair in describing this state as "a moderate degree of mental incapacity"?

The two situations described by Dr. Rose arise from the requirement that during the five-year period the patient must have been under continuous institutional care and attention. Under the Divorce (Insanity and Desertion) Act of 1958 a break of up to twenty-eight days is regarded as not interrupting continuous care and attention. It would be interesting to know whether there have been many cases in which a spouse has been prevented from seeking relief because of longer breaks in the continuity of care. If so, there might be a case for reducing the waiting period or for allowing for longer "breaks".

NON-CLINICAL TEACHING POSTS IN THE COMMONWEALTH

SIR,—The letter from Sir George McRobert fills me with despair and foreboding. It is terrible to think that after all the efforts of himself, the late Sir Bennett Hance, and Prof. C. A. Wells, Sir George has to advertise in the national medical press for retired people to come forward to fill the rewarding and interesting jobs that he has to offer—jobs that can be undertaken without loss of status at home and with every help and encouragement from the Commonwealth Relations Office while abroad.

I have already recorded in your columns [1] some of my own experiences in such a job. The difficulties must not be minimised, but I certainly found them well worth facing. I worked in Madras and had a difficult climate to contend with and colleagues with a very different background to my own, but to offset this a long tradition of British methods of work and of cooperation with British workers. Things may be different in other parts of the Commonwealth. However, with all deference to Sir George's far greater experience in this, I would have thought that retired men would have considerable difficulty in making the necessary physical and mental adjustments to such conditions. Such adjustments are vital to success and must be made quickly as in any case two years is not long in relation to the tasks that have to be undertaken.

The difficulty must be to find men of sufficient experience to undertake this responsible work, of sufficient age to be accepted as an adviser by their new colleagues, young enough to adapt themselves, and yet without family commitments. The retired man, of course, scores heavily over this last point, but surely others are to be found. The Commonwealth is used to British technical methods in many subjects and wants to continue in them, even if only because to change to others would waste valuable time and energy at this juncture. This change will become inevitable, however, with all its economic, social, and political consequences, if people to fill these jobs do not come forward.

1. Rewell, R. E. *Lancet*, 1958, ii, 574.

Heswall, Cheshire. R. E. REWELL.

RENAL ADAPTATION

SIR,—Many of our patients live or die without our treatment affecting the issue greatly one way or the other; a few live because of what we do for them; and some live on in spite of what we do to them. Sometimes, from this last group, we are given a chance to learn something of value, and the following case is reported to show how strenuously a single kidney will struggle on under great handicap.

The patient, a European woman, had undergone left nephrectomy in 1944, when she was aged 40, for a papilloma of the kidney pelvis. Unfortunately, I have found it impossible to trace her records, and no operative notes or histological reports are available. She had further hæmaturia in 1947, for which left ureterectomy and radium implantation were apparently carried out, but again no notes are available.

I first saw her in November, 1951, when she was referred for investigation of hæmaturia. Excretion urography showed good function of an apparently normal right kidney, but a filling defect of the left lateral wall of the bladder. At cystoscopy, I removed a sessile papilloma from the region where the left ureteric orifice would normally be found. It was about 1·5 cm. in diameter, and histologically was a transitional-cell carcinoma.

Although microscopically the tumour was not invading muscle, in view of the several recurrences, I decided that total cystectomy and ureterocolic anastomosis would give the best chance of cure. I performed this in two stages. At the initial operation, I used an extraperitoneal approach, and when I found that the previous operations and radium treatment had made it impossible to bring the pelvic colon over to the right side, and saw the cæcum in an easy position for anastomosis, I, in my ignorance, performed ureterocæcal anastomosis by the Coffey-1 technique. The patient made an uneventful recovery from this operation and from the total cystectomy two weeks later. Histological examination of the excised bladder confirmed the presence of transitional cell carcinoma of the left lateral wall, which did not appear to be invading muscle.

The main interest in this report lies in her subsequent progress: she has always lived some distance from town which has made close control or elaborate dieting impossible. But she has managed to continue in an "office job", and enjoy a moderately active life on a low salt diet, with sod. bicarb. drachm 1 q.d.s., plenty of fruit, and goat's milk.

She has attended occasionally since that time, and the relevant findings are summarised below:

March, 1952: Feels well. Has put on weight. B.P.140/90. No renal tenderness.

August, 1952: Feels well. Weight steady. Right kidney enlarged but not tender.

May, 1953: Admitted to hospital with sudden suppression of urine and hydronephrosis, presumably due to blockage of stoma by bowel contents, as symptoms rapidly relieved by enema.

August, 1953: Mild pyelitis treated with sulphonamide, but treatment discontinued because of oliguria. No retinopathy. B.P.160/110. Right kidney moderately enlarged but not tender now.

June, 1954: General health fair. Recent pyelitis. Has lost some weight.

April, 1956: Two recent attacks of pain in right flank, and some vomiting. Tires easily. Slight gradual loss of weight. B.P.140/95. Blood non-protein nitrogen 60 mg. per 100 ml. Excretion urogram: Fair concentration of dye. No obvious dilatation of kidney.

March, 1957: Frequent colicky abdominal pain recently, and constipation. Anorexia. Thirsty. Weight steady now. Blood non-

protein nitrogen 90 mg. per 100 ml. Blood-count normal. Barium meal examination: no abnormality noted.

November, 1958: Very frequent vomiting recently, but no dyspepsia. Looks well. B.P.160/100. Kidney now hardly palpable. No retinopathy. Blood-chemistry: Blood-urea 98 mg. per 100 ml., CO_2 combining power 20·1 mEq. per litre, chlorides (as Cl.) 116·2 mEq. per litre, sodium 149·5 mEq. per litre, potassium 7·1 mEq. per litre, calcium 5·9 mEq. per litre, total serum-proteins 7·0 g. per 100 ml., serum specific gravity 1025.

I am indebted to Dr. A. Kinnear for these estimations, and for the suggestion that improvement might be produced by a cation-exchange resin in the ammonium-potassium phase. The patient was given a month's supply of this resin, as transport difficulties made it impossible for periodic blood-examination, and it was felt that this was the longest period for which it would be safe for her to continue without further examination.

She has written recently to say that she feels much better, and has resumed her job, which she had relinquished last November.

Bulawayo, Rhodesia. W. HOUSTON.

BLOOD-SEROTONIN IN RHEUMATIC DISEASE

SIR,—Whereas many papers deal with the raised blood-serotonin in patients with metastasising argentaffinoma, little is known about 5-hydroxytryptamine (5-HT) metabolism in other diseases. Low 5-HT concentrations have been observed in patients with various blood disorders,[1–3] phenylketonuria,[4] uræmia,[5] gastric resections,[6] and cirrhosis of the liver,[6] but apparently no work has been done on patients with rheumatic disease.

We measured blood-levels of serotonin as follows. Bioassay of acetone blood-extracts was performed on the atropinised œstrous uterus of rats (method of Hardisty and Stacey [7]), and was repeated in the presence of 2-Br-lysergic acid diethylamide (10^{-7} g. per ml.).

The table shows that in comparison with the mean value of 60 healthy subjects, the serotonin content of blood was significantly lower in 8 patients with rheumatoid arthritis ($P < 0.01$), but in persons with rheumatic fever or osteoarthritis the blood-levels of serotonin were within the normal range. Prolonged treatment with corticosteroids raised the 5-HT levels of 5 patients with rheumatoid arthritis to nearly normal values.

SEROTONIN BLOOD-LEVELS IN RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER

—	5-Hydroxytryptamine	
	mμg. per ml. blood ±S.D.	mμg. per 10^{-8} blood-platelet ±S.D.
Controls, 60	117 ±6·5	71 ±4·3
Rheumatoid arthritis, 8 ..	33·5 ±7·1	29 ±8·8
Rheumatic fever, 9 ..	109 ±9·7	62 ±5·2

There is no evidence that thrombocytopenia was a major cause of the low serotonin values. Atrophy of the gastric mucosa, frequently observed in these patients, seems to have no importance either, as patients with treated pernicious anæmia or with chronic atrophic gastritis had normal blood-serotonin levels.[8] Perhaps a disturbance in tryptophan metabolism is responsible for a diminished 5-HT production in rheumatoid arthritis. We are pursuing this line of investigation.

E. SCHMID
F. SCHEIFFARTH
L. ZICHA.

Medizinische Universitätsklinik, Erlangen, Germany.

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AN EXAMINATION PAPER FOR . . . ?

SIR,—I feel that Miss Nuttall is incorrect in stating last week that there are not two mutually exclusive streams of nurse training, and I support Dr. Grant when he states (Aug. 29) that there are two quite separate nurse-training courses—that for State registration (S.R.N.) and that for enrolled assistant nurse (S.E.A.N.).

The length of the courses, the syllabuses, and the examination tests are quite different, and in the large majority of cases the training is carried out at separate hospitals. A small minority of training-schools offer both courses, but it is usually insisted upon that student nurses and pupil nurses shall not receive training together in the same ward. After registration or enrolment nurses and assistant nurses do indeed work together quite happily in the same nursing team in many of our hospitals. The important difference between the State-registered nurses and the enrolled assistant nurses is that the training and final examination test of the latter does not give full status of " nurse ", nor can the assistant nurse go forward in her profession to more advanced and special training, and she is debarred from the higher posts in nursing and administration.

I would submit that it is very important that these facts should be made quite clear both to the applicant for assistant-nurse training and to her parents, in order to avoid the disappointment of having to retrace her steps at the end of the two years and go back to the starting-point of the longer student training course should she desire to obtain full status and have the opportunity of advancement in her profession. This will mean a $4\frac{1}{2}$ years' training period which takes into consideration the 6 months' concession allowed by the G.N.C. which Miss Nuttall mentions.

Leeds. C. W. VINING.

SIR,—What does your correspondent, Dr. Grant, mean by the " natural feminine instincts " ?

Dr. Grant's words seem to suggest that little, if any, training, guidance, or education is needed for these instincts to flower into good nursing. There are enough complaints made about the quality of nurses to indicate that, whatever the endowment of potential nurses, some form of training and education is badly needed before they can be said to be good at their job. I rather suspect that your correspondent has in mind a vague picture of something warm, woolly, soft, sentimental, and " motherly "—what he wants is a nanny, not a nurse. In my experience (over twenty years in different sorts of hospital) most sick people, if they want mothering at all, don't want it from their nurses. They want a kind competent nurse to do for them the unpleasant and embarrassing things that need doing and which they would prefer their loved ones not to do: then they need the companionship and petting of their loved ones when nursing tasks are done. Nurses themselves often mistakenly believe that their patients want mothering—or more accurately " smothering ". Some of them are quite incapable of leaving the sick person alone for five minutes; they must always be fussing about doing things for them. They are, in fact, using their patients as substitute children; and I can't help thinking that these frustrated mothers would make very bad parents: at least their patients eventually escape from them—their children never would.

And why " feminine " instincts? It is news to me to hear that instincts have sex. Moreover, I have met in my career numerous perfectly normal men—mostly contentedly married and with children of their own—who are excellent nurses, both technically and from a point of view of personality.

Tooting Bec Hospital, London, S.W.17. UNA V. BUDGE.

SIR,—If the medical education of nurses is inefficient or maldirected, we as doctors are responsible. The correspondence in your columns should lead us to consider whether we are adequately discharging our responsibilities.

Much of the confusion arises from a lack of definition of objectives. As a result, textbooks for nurses are written from the standpoint of the doctor-teacher rather than of the student-nurse. Anatomy is separated from physiology and based on the dissecting-room, a traditional approach for doctors but one completely foreign to the nurse. A nurse deals with functional and surface anatomy, and to separate these from physiology is clearly artificial. Any greater anatomical depth should probably be based on radiology. Again, the artificial division of medicine into internal medicine, surgery, and gynæcology is doubtfully justifiable in the education of a doctor, but has no justification in the education of a nurse. The factual content of a nurse's medical course should be the minimum necessary to explain and illustrate principles and concepts. If a nurse wishes to pursue a particular subject more deeply she can always consult a medical textbook.

What is needed in nurses' education is clear thinking and a definition of objectives. Some of your readers may be unaware of the revolution that has been achieved by these means in the teaching of first aid. If so, they should read Dr. Robert Mustard's small volume on the Fundamentals of First Aid written for the Canadian Order of St. John.

London, W.1. DAVID H. PATEY.

ADMINISTRATION OF DRUGS IN HOSPITALS

SIR,—In his system to overcome the difficulties and dangers of drug administration in hospitals, Mr. Fowler (Sept. 5) sets out with five good reasons to condemn the ward medicine list. But this is not his final judgment. On second thoughts he believes that the worst features are merely "drawbacks" which he eliminates. This leaves him with "its potential advantages", from which he develops a new medicine list, which is just as dangerous as those he condemns.

The Aitken Committee were aware of more serious objections to a medicine list than those enumerated by Mr. Fowler.

These objections arise because a medicine list is not necessarily, and in practice is not likely to be, an accurate copy of the prescriber's instructions as recorded by him on the treatment sheet. Accurate copying is an extremely difficult art. Those skilled in the art (copy typists and compositors) make an average of three mistakes in each page copied; hence the need for galley-proofs and proof readers. Those unskilled in the art—and a ward sister would not claim this skill—are likely to make more than three mistakes a page. It follows that a medicine list is likely to contain errors in copying. But there may also be errors of interpretation; indeed Mr. Fowler himself states that "to entrust this [the interpretation of a prescription] to any nurse is to court disaster". An error is also likely to be perpetuated because a medicine list is an exclusively nursing document; the pharmacist never sees it—he might not be able to interpret it if he did—neither is it scrutinised by the prescriber who may remain in ignorance of the errors of copying, interpretation, and omission to which his patient is exposed.

Mr. Fowler, unlike the Aitken Committee, may be unaware of the risks arising from errors of omission on the medicine list, which have resulted in serious and even fatal mishaps. They may occur when a change of treatment is required. The prescriber may give his new instructions in writing on the treatment sheet. The action that follows will depend upon whether and when the requisite amendment is made to the medicine list: the instructions may be implemented promptly or they may be deferred or even ignored.

Mr. Fowler criticises the recommendation of the Aitken Committee that the prescription—the original document bearing up-to-the-minute instructions for the patient's treatment—should be the focus of the checking system for nurses administering drugs. If he is still in doubt of the validity of the recommendation, may I ask him whether as a pharmacist he would be prepared to accept the risks of dispensing drugs from the medicine list he advocates? If he would not, is it reasonable to expose patients to such risks at the hands of the nursing staff?

Churchill Hospital, Headington, Oxford. W. TRILLWOOD.

SERUM-MAGNESIUM AND CORTICOSTEROIDS IN CHRONIC ALCOHOLISM

SIR,—We have already shown [1] the extent to which fat embolism occurs in patients who have fatty livers or cirrhosis, and who in life may have shown signs of delirium tremens. Subsequently we published [2] the results of several clinicopathological studies in which sputum from patients admitted in alcoholic states was examined serially for fat.

Flink and his coworkers [3 4] have concluded that a low serum-magnesium level is at least partly responsible for the clinical picture of chronic alcoholism, and this has been confirmed by Suter and Klingman.[5] As Flink pointed out, the relation between the levels of serum-magnesium and features such as muscular twitching, tremor, and hallucinations is not simple. Some patients with low serum-magnesium levels have no symptoms or signs, while others with normal levels may be seriously ill.

At first we thought that these two hypotheses might be related, possibly by fat adsorbing magnesium in some way, but animal experiment failed to confirm this. However, in delirium tremens a state of extreme stress is often reached, and thus we considered the possibility that adrenocortical hormones played some part in the change of magnesium levels. One of the earlier papers on aldosterone [6] indicated that this lowered serum-magnesium, presumably by impairing resorption of magnesium by the renal tubules. It has also been demonstrated that, after administration of corticotrophin, urinary excretion of magnesium is greatly increased after a lag of some days.[7] Loraine [8] found that plasma concentrations of 17 : 21 dihydroxy–20 ketocorticosteroids are increased after major surgery and were very high in patients with postoperative shock. It should be remembered that fat embolism is almost invariably associated with shock [9] and thus the association between shock, steroid hormones, and magnesium metabolism becomes less tenuous. The relation between lipids and serum-magnesium as described by Bersohn and Oelofse [10] is not direct, since they found that in the Bantu the levels of serum-cholesterol were lower while serum-magnesium was higher than in European subjects.

The method for magnesium estimation described by Neill and Neely [11] was used with modifications as follows:

0·1% w/v polyvinyl alcohol in distilled water in place of gum ghatti.

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0·01% w/v titan yellow (B.D.H.) instead of 0·5% w/v titan yellow. 7·5% w/v NaOH instead of 4N.NaOH.

Readings of optical density were made in the Spectronic 20 spectrophotometer at 540 mμ.

To avoid possible errors such as variations in reagents, temperature, &c., the estimations were made in batches after identical conditions of storage at the end of each experiment.

Twenty-two rabbits were given emulsified fat in saline intravenously. In sixteen of these no appreciable effect was produced by the injection of 0·2–0·5 ml. of the preparation, whether the fat was an alcohol or ether extract, partially split or not, or taken from animals living normally or under high oxygen tensions. Two animals given 50 mg. cephalin intravenously failed to show any effect, but four animals did show some depression of serum-magnesium (3·8–2·4 mg.; 3·7–2·6 mg.; 2·15–1·4 mg.; and 2·4–1·2 mg. respectively in 2 hours). All samples of fat used in these came from a rabbit dying of hyaline-membrane disease after prolonged exposure to high tensions of oxygen. Although the fat in these animals is grossly altered, appearing pale and œdematous, and although similar samples were obtained from other animals, the use of further samples did not reduce serum-magnesium levels. We now think that the adrenal gland was accidentally included in the emulsion made from this original sample.

Six rabbits were treated with 20 mg. cortisone acetate intramuscularly twice daily for a period up to $3^1/_2$ days. In all there was a continual fall in the levels of serum-magnesium (table I) which was most marked between 48 and 72 hours.

TABLE I—SERUM-MAGNESIUM CHANGES AFTER ADMINISTRATION OF CORTISONE

Rabbit	Serum-magnesium (mg. per 100 ml.)	
	Basal level	Level at end of experiment ($2^1/_2$–$3^1/_2$ days)
1	3·6	1·6
2	2·0	1·6
3	2·5	2·1
4	3·5	2·1
5	2·5	1·8
6	2·2	1·7

Results with intravenous corticotrophin were equally striking (table II).

It would appear from this series of experiments that both cortisone and corticotrophin definitely lower the level of serum-magnesium in rabbits. There is also some evidence that some steroid hormones may have a similar effect in man. The sequence of fat embolism, followed by

TABLE II—SERUM-MAGNESIUM CHANGES AFTER ADMINISTRATION OF CORTICOTROPHIN

Rabbit	Dosage of corticotrophin (units)	Serum-magnesium (mg. per 100 ml.)	
		Basal level	Level at end of experiment ($1^1/_2$–$2^1/_2$ days)
1	25 b.d.	3·4	2·7
2	25 b.d. (day 1 only)	2·0	1·3
3	25 b.d. (day 1 only)	2·5	1·8
4	25 (one dose only)	2·6	1·7
5	25 (one dose only)	2·4	1·7
6	25 b.d.	3·7	2·4

"shock", followed by increased output of adrenocortical hormones causing lowered serum-magnesium may be advanced as a unifying hypothesis of the pathological and biochemical patterns in delirium tremens. We are at present investigating this and other facets of adrenocortical activity in chronic alcoholics.

This work was supported in part by a grant received from the Alcoholism Research Foundation of Ontario.

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Obituary

WALTER HAWARD

Kt., O.B.E., M.B. Durh.

Sir Walter Haward, a former director-general of medical services at the Ministry of Pensions, died on Sept. 2 at the age of 77.

He studied medicine at the University of Durham and at St. Thomas's Hospital, and after qualifying in 1904 he held house-appointments there before settling in general practice in Kilburn. During the 1914–18 war he served in the R.A.M.C. with the rank of major, and he was in charge of medical divisions of military hospitals in Salonika. During this appointment he was for a time attached to the Serbian Army, and for his work he was appointed to the Order of St. Sava (4th class). He was also mentioned in despatches.

Stonemen

On demobilisation in 1919 he joined the medical service of the Ministry of Pensions as deputy controller, and he was promoted to principal medical officer in 1925, to director in 1938, and to director-general in 1942. He retired in 1947. He was appointed O.B.E. in 1938, and he was knighted in 1944. From 1947 to 1950 he was an honorary physician to the King.

Of Haward's work at the Ministry, C. G. M. writes:

"Haward was called at a critical time during the war, by the unexpected death of his predecessor, to assume the duties of director-general of the medical services of the Ministry of Pensions. He was thus faced immediately with a task of the greatest responsibility, which involved the rapid expansion of a medical service normally in low gear since twenty years had elapsed from the first world war and claims to war disablement had lessened with the passage of time. Not only was there a need for augmentation of a headquarters and medical boarding system, but there was also the need to quickly establish and staff a hospital service to deal with an unpredictable flow of casualties. Moreover, each of these new establishments was vulnerable to air-raids and every contingency had to be kept in mind. Throughout the whole of this period of expansion, development, and innovation, not to mention the institution of appeal tribunals, liaison with other Government and Service Departments, and the general control and replenishment of a medical service constantly depleted by recruitment of doctors for the Forces, Haward managed to keep his poise and an unfailing concern for the welfare of his staff."

In 1905 Sir Walter married Louisa Ayton Mann, who survives him with a son and three daughters.

EDWARD STEPHENS DUTHIE

M.B., Ph.D., M.Sc. Dubl., D.P.H.

Dr. Edward Duthie, director of pathology at Southampton, died on June 9 at the age of 52.

He began a brilliant academic career by winning a sizarship in mathematics to Trinity College, Dublin. He won first-class honours and a gold medal with his arts degree in 1929, and he graduated M.B. and M.SC. in 1930 and PH.D. three years later. He received a Rockefeller fellowship in 1931; in 1933 he was appointed Graham scholar at University College Hospital Medical School, where, under A. E. Boycott, he developed his talents as an experimental biologist. It was typical of Duthie that he should want to broaden his knowledge of pathology by closer contact with clinical work, and with this aim he became assistant pathologist at the University of Sheffield in 1936.

His work on mucus secretion, begun in Dublin under Gatenby, had attracted the attention of Florey, who invited him in 1937 to join his team at the Dunn School of Pathology, Oxford, where he was appointed university demonstrator in pathology and May reader in medicine.

In 1940 Chain and Duthie published important papers on hyaluronidase and on a polypeptide involved in inflammation. Duthie was unwilling to remain in academic work during the war, and was unfit for active service, so he became hospital pathologist at Northampton. He returned to Oxford in 1943 to help Cairns in the treatment of head injuries. The production of penicillinase, which he developed at this time, greatly facilitated the bacteriological control of penicillin therapy.

Duthie left Oxford early in 1946 to take charge of the serum department of the Lister Institute. In 1948 he was appointed deputy director of pathology at Southampton, becoming director in 1952.

C. H. L. writes:

"During the last ten years of his life Duthie worked himself to death. He had a heavy load of clinical and administrative work, enough to exhaust most men, but despite ill health he continued his research, and became engaged in a campaign to prevent cross-infection in hospitals. His major achievement while at Southampton was the purification of staphylocoagulase—the first blood-clotting substance ever to be purified. Only those who have seen the cramped quarters in which he worked and who know the volume of routine clinical pathology that was being done simultaneously will appreciate what an achievement this was. He also established the independence of bound coagulase, or 'clumping factor' as he preferred to call it, from the free coagulase produced by staphylococci.

"He appreciated the best in art, music, and literature, and also in people. He made friends wherever he went, and was singularly loyal and helpful to all who worked with him. He was generous to all who needed his help, especially to refugees. One of the outstanding experimental pathologists of his time, he was also a man whose qualities evoked the admiration and affection of all who knew him."

HARRY WALKER

L.R.C.P., F.F.A. R.C.S., D.A.

Dr. Harry Walker, consultant anæsthetist to the South and North Tees-side hospitals, died on July 18 at the age of 39.

Dr. Walker was the eldest son of a Middlesbrough dentist, and he qualified in Edinburgh in 1942. Afterwards he held the post of house-surgeon at the North Riding Infirmary, Middlesbrough. During the late war he served with the R.A.M.C. in Burma and Java, and on demobilisation he entered general practice in Middlesbrough. He took the diploma in anæsthetics in 1948, and shortly afterwards gave up general practice when he was appointed to his consultant post. For some years he had acted as honorary secretary to the medical staff committee at Hemlington Hospital, and he had attended a meeting of the committee only a few hours before his sudden illness. He is survived by a widow and three young daughters.

Sir ROBERT YOUNG

T. V. L. C. writes:

"I first met R. A. when I went to the Middlesex from Kings in 1934. One evening we were showing off the new Collins' X-ray diagnostic department which we had just created, and among the honoraries and visitors there was this most courtly and distinguished gentleman accompanied by an equally stately lady. As he shook hands with me—he always did this whenever he came to discuss any problems in the department—he immediately turned to his wife and said, 'My dear, let me introduce you to Dr. C., who has just joined us.' And I—a newcomer—felt so much at home.

"I have never met any chest physician who read so much from the physical examination, which Young performed so carefully and methodically, without any haste. For him the patient always came first. One day I watched him look at a patient, percuss, palpate him, and auscultate and then, putting a finger on a spot on an intercostal muscle, he said, 'There is a band of adhesions here.' And true enough, when we screened the patient there was this band of adhesions at that identical spot.

"He was a great connoisseur of food and especially of wines, and enjoyed to the utmost all the dinners he attended, whether at a City company, in a friend's home, or on a Saturday evening at the Savage, where he was a senior member for a very long time. He enjoyed these Saturday evenings, not only for the food and wine but also for the good fellowship and wonderful singing by Brother Savages, and his evening was made if Benno Moiseiwitsch happened to be there and played. Even on May 30 when he was not by any means well, he made a point of attending the dinner to celebrate Mark Hambourg's 80th birthday.

"R. A. was always courteous and courtly, honest and sincere, and a true and loyal friend. I have never known him to say a harsh word or to speak ill of anyone. Like all great men he was most approachable: everyone—student, houseman, or consultant—was sure of a kindly and sympathetic ear on any matter, clinical or otherwise, and so his advice was widely sought. His knowledge of silver, porcelain, and antiques was wide, and he knew more of the history of London than anyone I knew. It was one of his great joys at weekends to wander through the City and visit some little-known historic spot."

T. L. H. writes:

"One of the great physicians of his day, R. A. excelled as a clinical teacher, particularly in his demonstration of physical signs. He had the hands of an artist and his percussion was a thing of perfection. He outgrew his generation but always kept abreast of modern advances, welcoming the new, while retaining the best of the old. There was no limit to his interests and his mind ranged widely and curiously. He took infinite pains in all he undertook—in clinical teaching, giving advice on a difficult problem, medical and personal, preparing an address, selecting a menu, or choosing a wine. He was an inveterate collector of bric-à-brac and his flat in Down Street was literally crammed with objects of art and curios, which he delighted in showing, with many a good tale of their origin and purpose.

"His capacity for friendships was unlimited and he kept them in constant repair, always retaining his interest in his former pupils and their work. His companionship was delightful. He liked to talk, and he talked wittily and well. His zest for life was enormous and he maintained it to the end. Great physician, wise counsellor, and faithful friend, ave atque vale."

Public Health

Infectious Diseases in England and Wales

Disease	Week ending August				
	1	8	15	22	29*
Diphtheria	6	2	3	..	5
Dysentery	398	365	434	385	393
Encephalitis:					
Infective	6	..	8	2	3
Postinfectious	1	2	2	3	1
Food-poisoning	293	250	340	250	328
Measles, excluding rubella	6189	4611	4036	2781	1854
Meningococcal infection	13	17	8	16	15
Ophthalmia neonatorum	17	27	15	31	20
Paratyphoid fever	3	3	10	17	19
Pneumonia, primary or influenzal	146	130	137	115	125
Poliomyelitis:					
Paralytic	35	23	28	34	19
Non-paralytic	23	17	18	24	17
Puerperal pyrexia	207	182	200	214	206
Scarlet fever	643	465	367	327	265
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	462	354	426	423	396
Meninges and C.N.S.	5	3	3	2	3
Other	58	50	54	51	47
Typhoid fever	..	3	3	8	5
Whooping-cough	711	616	798	777	863

* Not including late returns.

Notes and News

MEMORABLE LIVES

THE main twenty-two volumes of the *Dictionary of National Biography* which were completed between 1885 and 1900 contain some 30,000 biographies and cover the years up to 1900. Since then the *Twentieth Century D.N.B.* has kept the record up to date with supplements for each decade. The latest of these,[1] for 1941–50, has 725 biographies. Though the deaths of all these men and women lay within this narrow span, their births fell between 1845 and 1918, and their achievements were scattered over some seventy strenuous and exciting years. Arbitrary selection and alphabetical arrangement cannot provide a continuous narrative, but the haphazard glimpses they offer are stimulating and instructive.

The first medical name is Joseph Arkwright, the last Warrington Yorke. Between them lie many others who recall new discoveries, new specialties, and new ways of practice. The name of the venerable Sir Thomas Barlow, for instance, recalls the disappearance of scurvy and rickets and the growth of pædiatrics, and this theme is developed by the biographies of Sir Frederic Still and Sir Leonard Parsons. The importance of nutrition in many diseases of childhood adds points to the biography of Sir Gowland Hopkins, a Nobel laureate, the discoverer of vitamins in the laboratory. Banting's work on insulin is another example of the spectacular contributions to clinical medicine made in these years by the laboratory, and of how much we owe to such men as Sir Thomas Lewis, " the advocate of clinical science ". And so the chain goes on. The name of Girdlestone recalls not only the growth of a new specialty—orthopædics—but also the munificent establishment of the Nuffield chairs at Oxford; that of John Ryle, among other things, the institution of chairs of social medicine; while C. S. Myers' life reminds us that the first English laboratory of experimental psychology was only set up in Cambridge in 1912. The life of Lord Dawson of Penn shows how much legislation in this period has touched the interest and responsibilities of medicine. These years also saw the expansion of the public-health and preventive services; and Sir George Newman, the first chief medical officer of the Ministry of Health, stands appropriately next to Sir Arthur Newsholme, the last medical officer of the Local Government Board. The biography of Sir Thomas Oliver, a pioneer of industrial medicine and of safeguards against industrial hazards, notably lead, warns us that sizeable gaps still remain. Medical historians include Sir William Hale-White, whose studies of Guy's Hospital have the charm to be expected from the son of Mark Rutherford, and to Sir Bernard Spilsbury's forensic and scientific achievements is demurely added the literary footnote that he has become the " prototype of the doctor detective in modern fiction ".

Allowances for Some S.H.M.O.s

The Minister of Health has approved the proposal of the Medical Whitley Council (committee B) that certain senior hospital medical officers who hold appointments which have been graded as consultant posts shall become eligible for an allowance of £550 per annum. The Minister asks hospital boards to set up special committees to review applications for this grant. Claims, according to the Ministry's memorandum (HM[59]81), should be " subjected to exacting scrutiny ".

British Medical Association

Dain Fund—During 1956–57 the Fund spent £3500 helping 31 cases including 12 new ones. The income for the year, after providing for long-term needs, was £2800 and the grants made therefore exceeded the available income by about £700. The Trustees have so far been able to help all those they considered to be in need, but if applications continue at the present rate they fear that they will be unable to do so without serious encroachment on the capital investments of the Fund, unless more donations are received each year.

1. Dictionary of National Biography 1941–50. Editors: L. G. Wickham Legg, E. T. Williams. London: Oxford University Press. 1959. Pp. 1031. £5 5s.

College of General Practitioners

In the August issue of their journal the council have announced their reluctant decision to abandon the plan to build a new home for the college on the south side of Lincoln's Inn Fields alongside the Royal College of Surgeons. The original plan could not be realised, and consequent difficulties have arisen about financing the project, as well as about the length of the lease offered. For the present therefore the college will remain in its temporary home at 41, Cadogan Gardens (a house with eleven rooms). Later it hopes to find larger headquarters, and arrangements for launching an appeal for an endowment fund are well advanced.

Heating and Ventilation

The British Occupational Hygiene Society will hold a conference on this subject on Wednesday, Nov. 4, at the Institute of Mechanical Engineers, Westminster, London. Non-members may attend, and further particulars may be had from Dr. D. Turner, Associated Ethyl Company, Ltd., Ellesmere Port, Cheshire.

New British Standards

Draft proposals for three new British Standards—for pressure steam sterilisers of small size (CZ[SGC]9407), Harrison's bowl forceps (CZ[SGC]9406), and rectangular metal sterilising containers (CZ[SGC]9405)—have been announced. Any comments on these should be sent to Mr. W. S. Hodges at the British Standards Institution (2, Park Street, London, W.1) before Sept. 21, 22, and 23 for the three articles, respectively.

Sir Hugh Beaver will give the opening address of the session at St. George's Hospital Medical School on Friday, Oct. 2, at 3 P.M.

Dr. John Lockwood, Master of Birkbeck College, will give the inaugural address of the Royal Free Hospital School of Medicine on Friday, Oct. 2, at 3 P.M., at the Senate House, London, W.C.1.

Prof. P. A. Bastenie, head of the medical clinic of the Hospital St. Pierre, Brussels, has been appointed visiting professor of Belgian studies in the University of London for 1959–60.

The annual dinner of the Yorkshire Association of the Graduates of Glasgow University will be held on Friday, Oct. 23, at Leeds University. Further particulars may be had from Mr. James Wishart, 33, Manor Row, Bradford, 1.

Appointments

ANDREWS, P. S., M.D. Cantab.: consultant pathologist, Kettering/Northampton area department of pathology.
BOWEN, D. R., M.B., B.SC. Wales: M.O. (S.H.M.O.), mass radiography service and Cardiff chest clinic.
BURROWES, H. P., M.B. Lond., D.P.H.: senior M.O. for mental health, Bradford.
GREIG, ANNE C. V., M.B. Glasg., D.P.H.: assistant divisional M.O., Lancashire County Council (Fylde area).
JONES, A. P., M.B. Wales, D.P.H.: deputy M.O.H. and deputy principal school M.O., Coventry.
OLDFIELD, JAMES, M.B. Durh., F.R.C.S.: consultant surgeon, clinic no. 1, South Tees-side group of hospitals.
SKONE, J. F., M.D. Lond., D.P.H., D.C.H., D.I.H.: deputy M.O.H., deputy principal school M.O., and deputy port M.O., Bristol.
THOMPSON, NOEL, M.B. Durh., F.R.C.S., B.D.S.: consultant plastic surgeon Stoke Mandeville Hospital, Aylesbury.
WALLING, K. E., M.B. St. And., D.P.H.: assistant M.O.H., Dundee.

Colonial Appointments:

CLAY, R. A., M.B. Lucknow: district M.O., Dominica.
DAVIS, E. J., M.B.: M.O., Brunei.
HEAP, S. W., M.B. Lond.: M.O., British Honduras.
HEBRON, A. S. B., L.R.C.P.E.: senior M.O., Sierra Leone.
MACKAY, D. L., M.B. Edin., D.T.M. & H.: M.O., Gambia.
O'SULLIVAN, J. L., M.B. Cantab.: M.O., Uganda.
PITT-PAYNE, BRUCE, M.R.C.S.: M.O., South Pacific Health Service.
TENNANT, E. R. H., M.B. Aberd., D.C.H., D.P.H.: M.O., North Borneo.
UKU, J. M., M.B. Glasg., D.C.P.: specialist (pathologist), Ministry of Health, Federation of Nigeria.
VAN DE LINDE, P. A. M., M.B. Lond., D.P.H., D.I.H.: senior health officer (medical officer of health new territories), medical and health department, Hong Kong.
WRIGLEY, E. J., M.B. Lond.: M.O., Northern Region of Nigeria.

Births, Marriages, and Deaths

DEATHS

HAWARD.—On Sept. 2, at Queen Mary's Hospital, Roehampton, Sir Walter Haward, O.B.E., M.B., aged 77 years, of The Wold, Woldingham, Surrey, husband of Lulu.